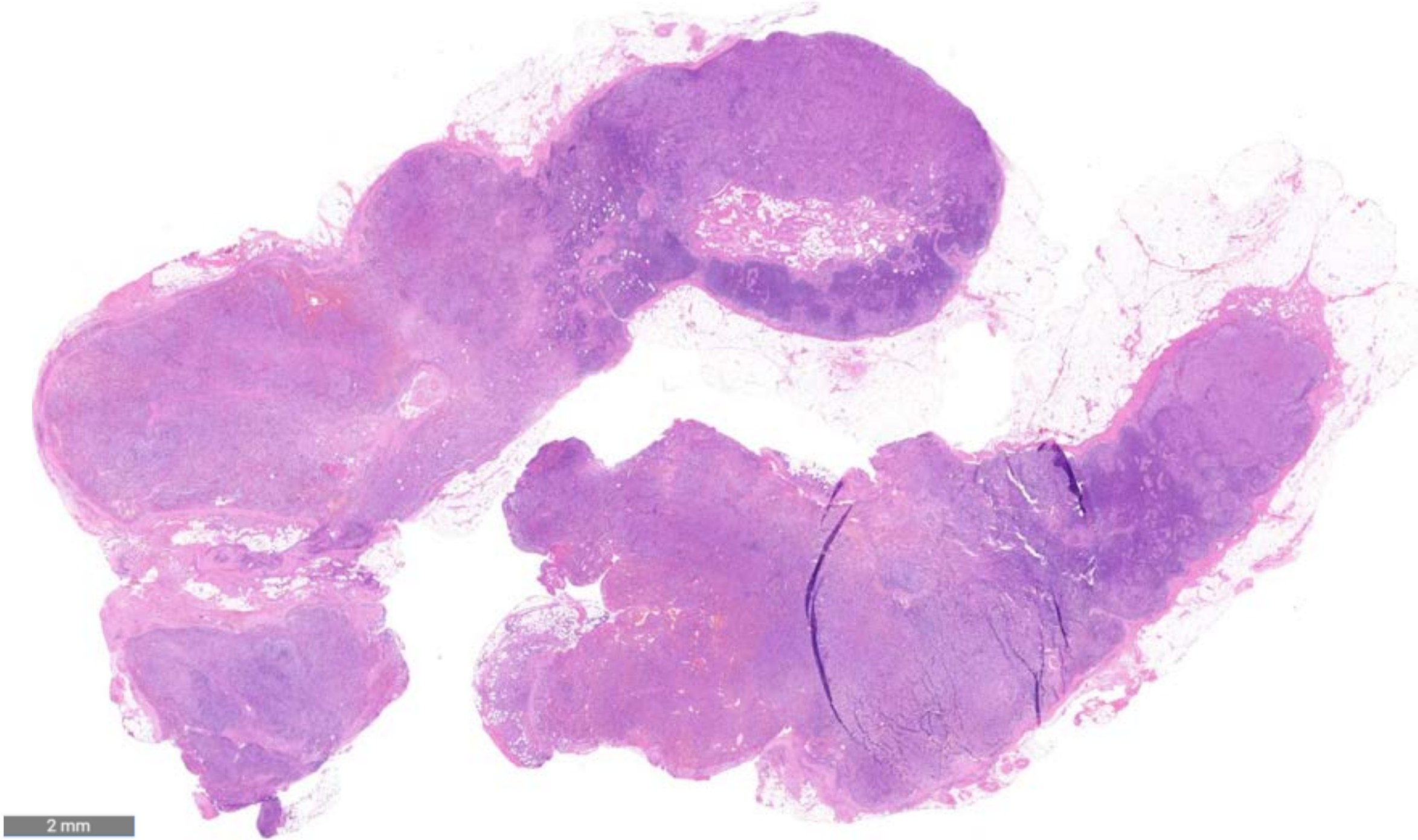
Case #3

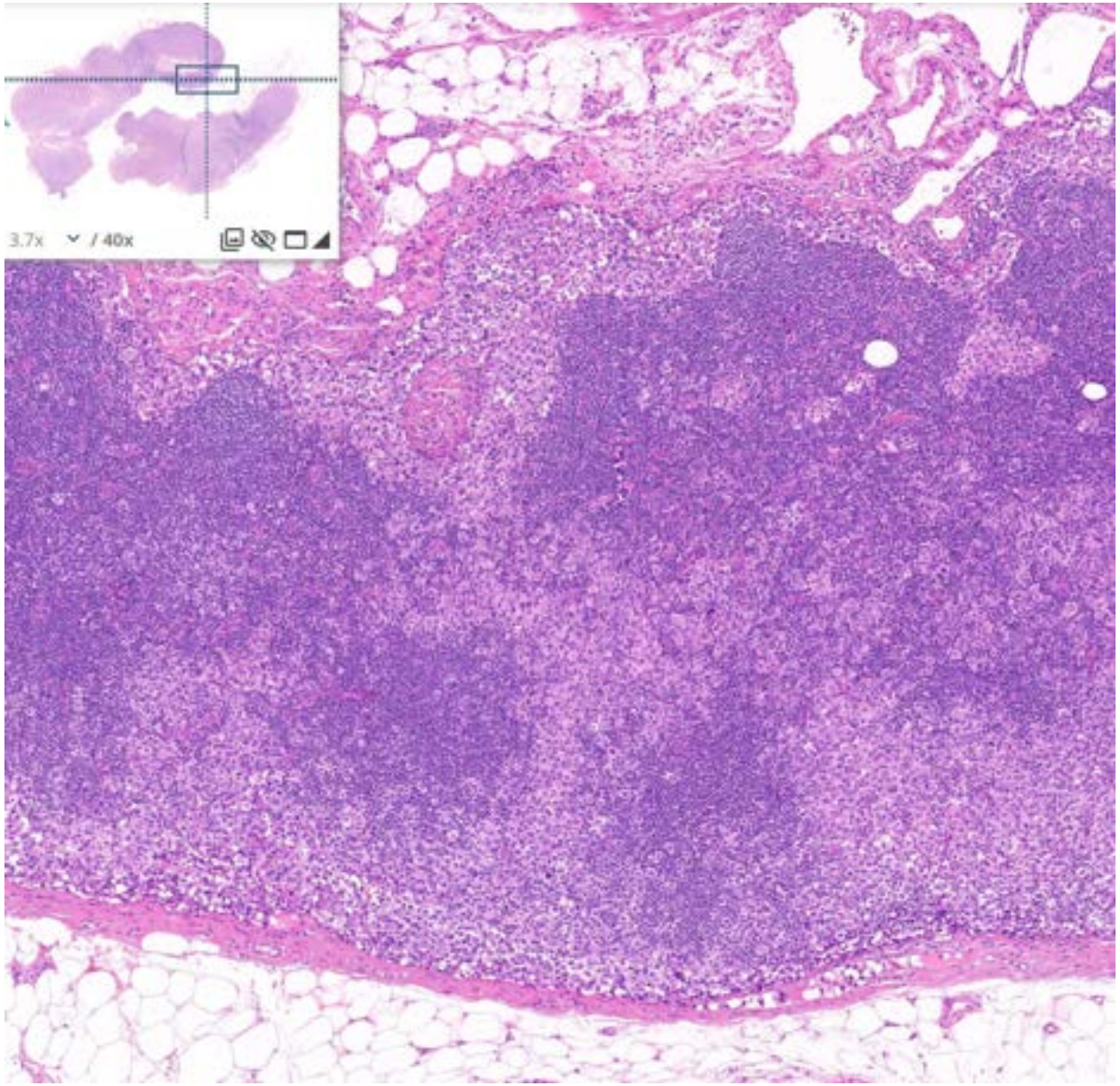
Kelly Bowers, DO, MPH
Staff hematopathologist
5/27/2026

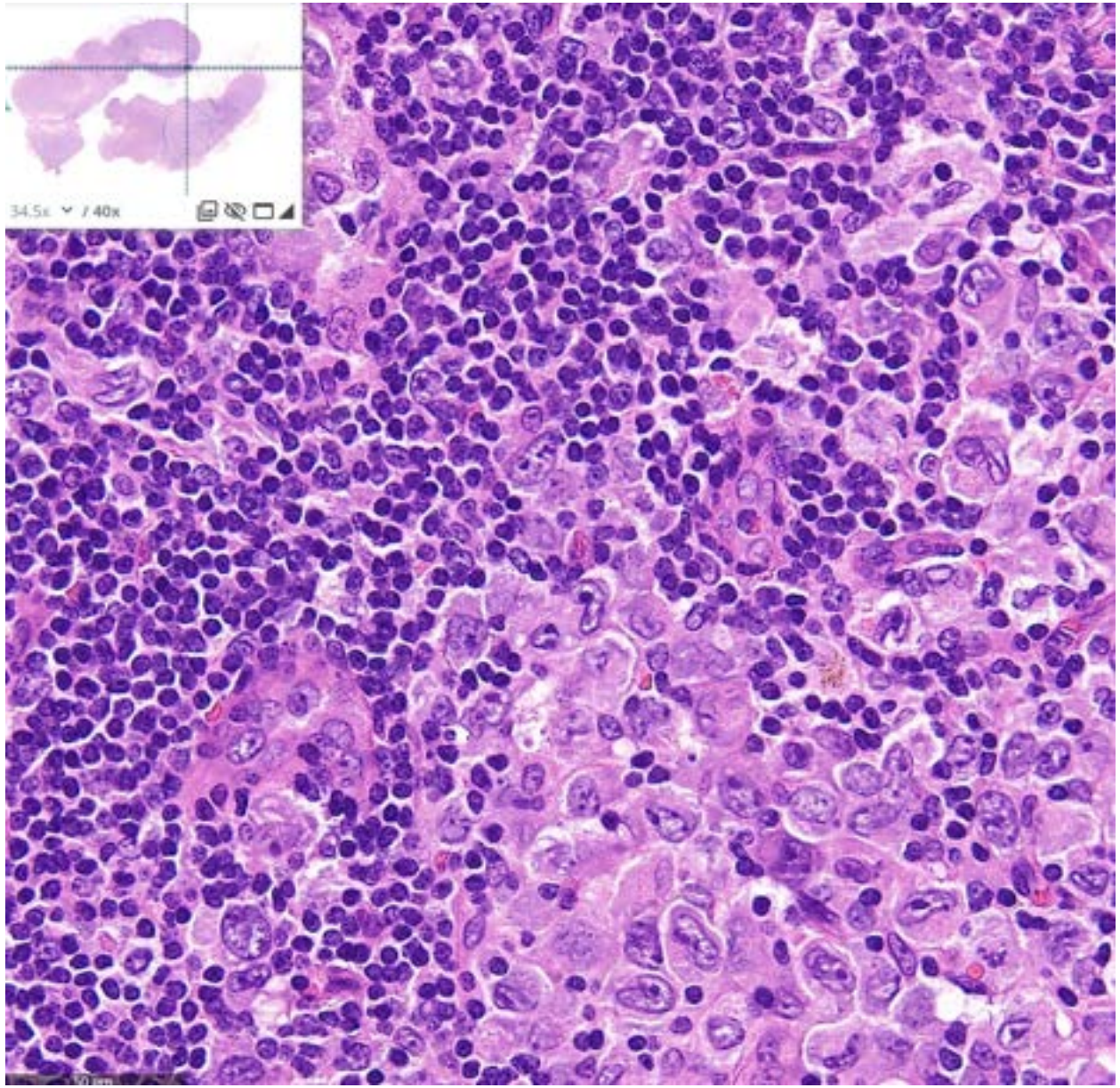
Cleveland Clinic

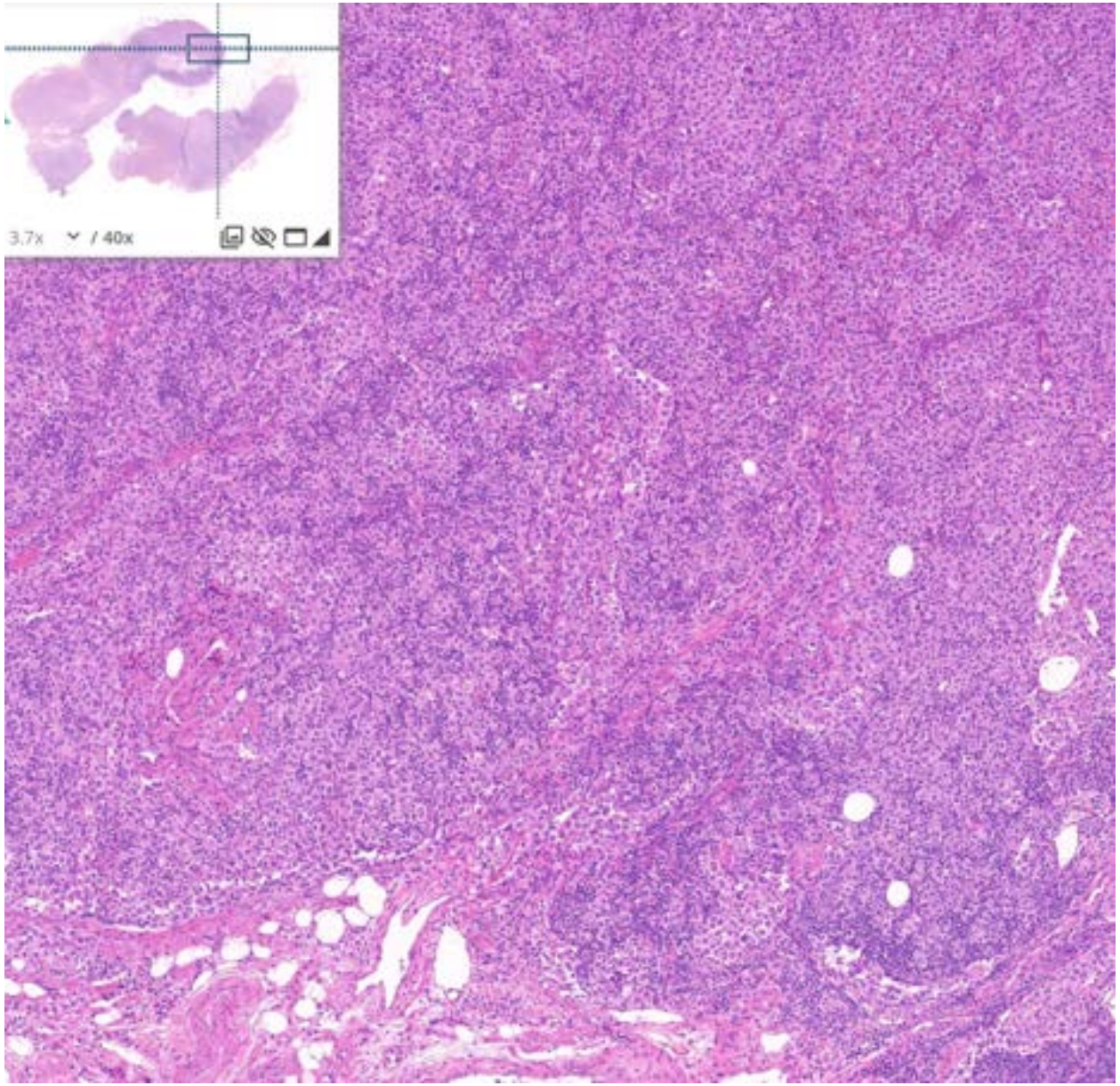
Clinical History

- 58-year-old male presenting with inguinal lymphadenopathy
- Inguinal lymph node excision performed


2 mm


3.7x / 40x


34.5x / 40x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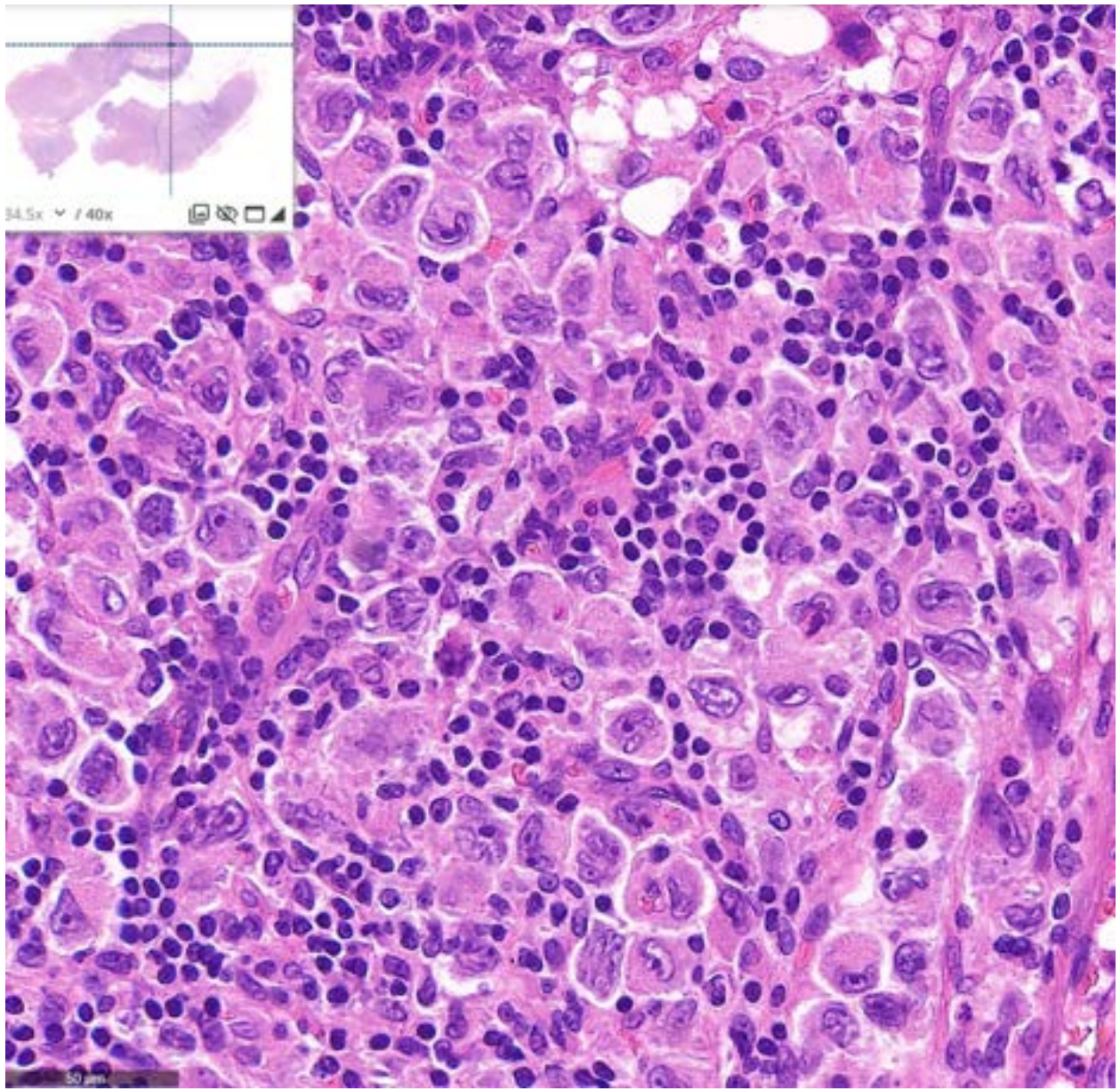
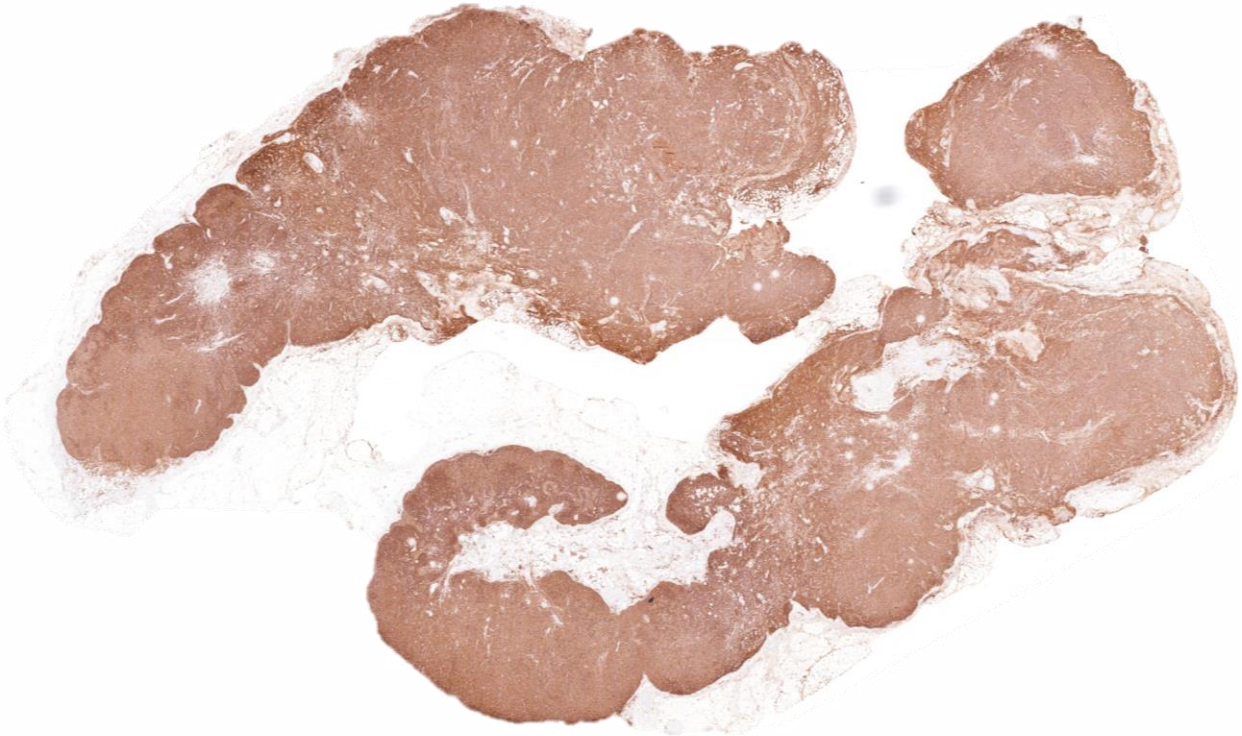
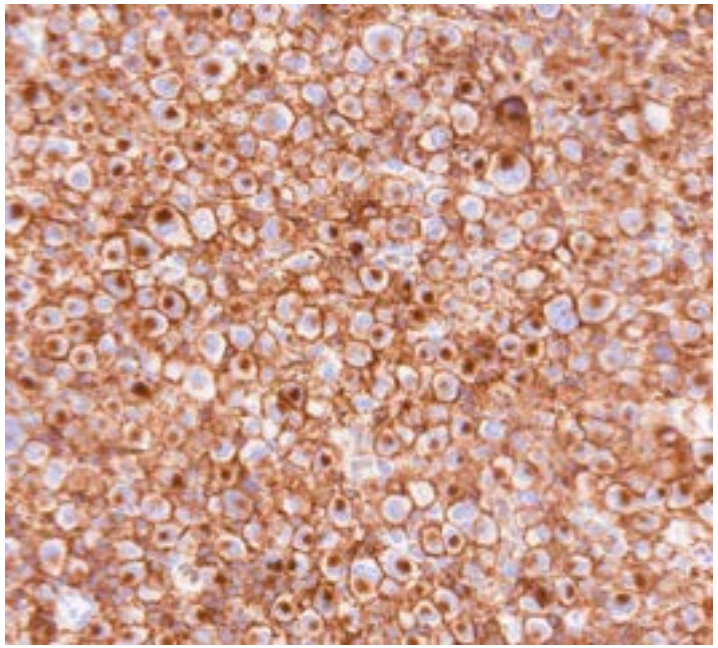
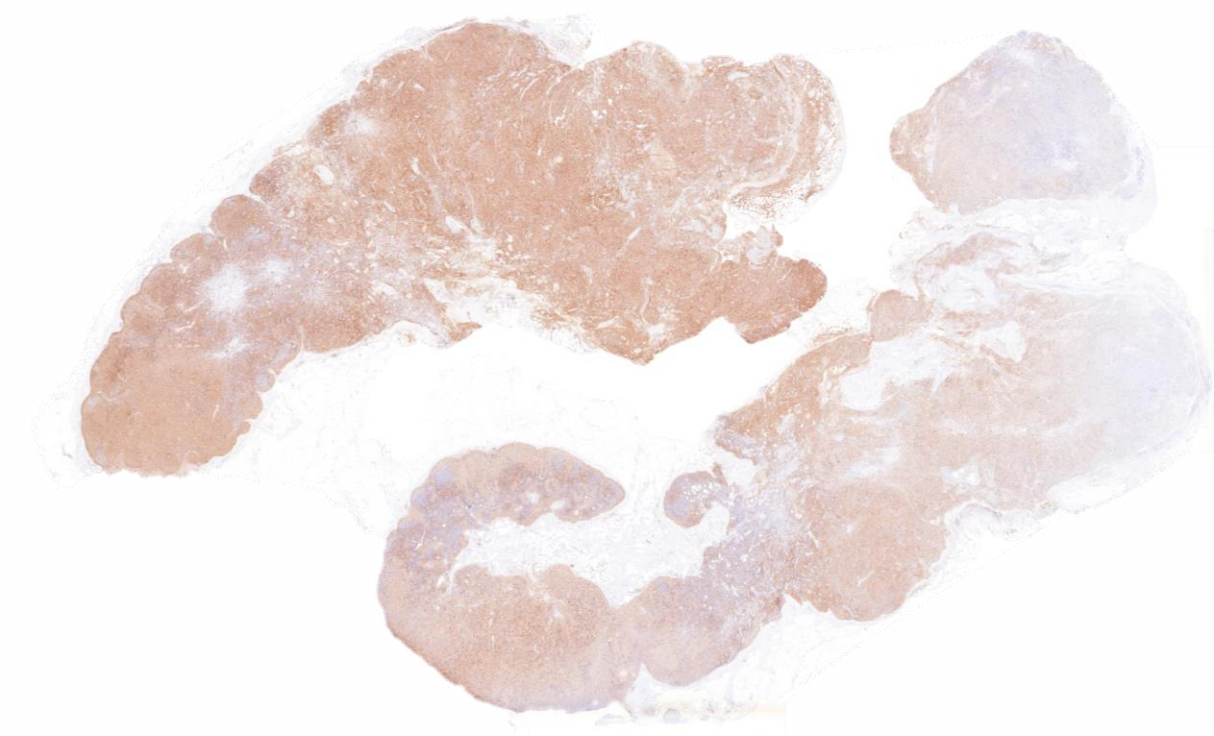

34.5x / 40x
50 µm

Differential diagnosis by H&E morphology?

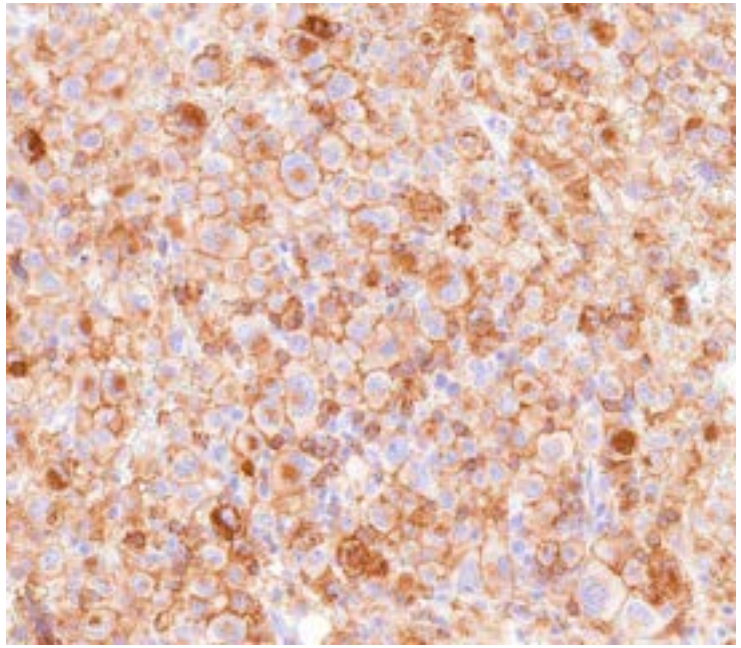


CD45

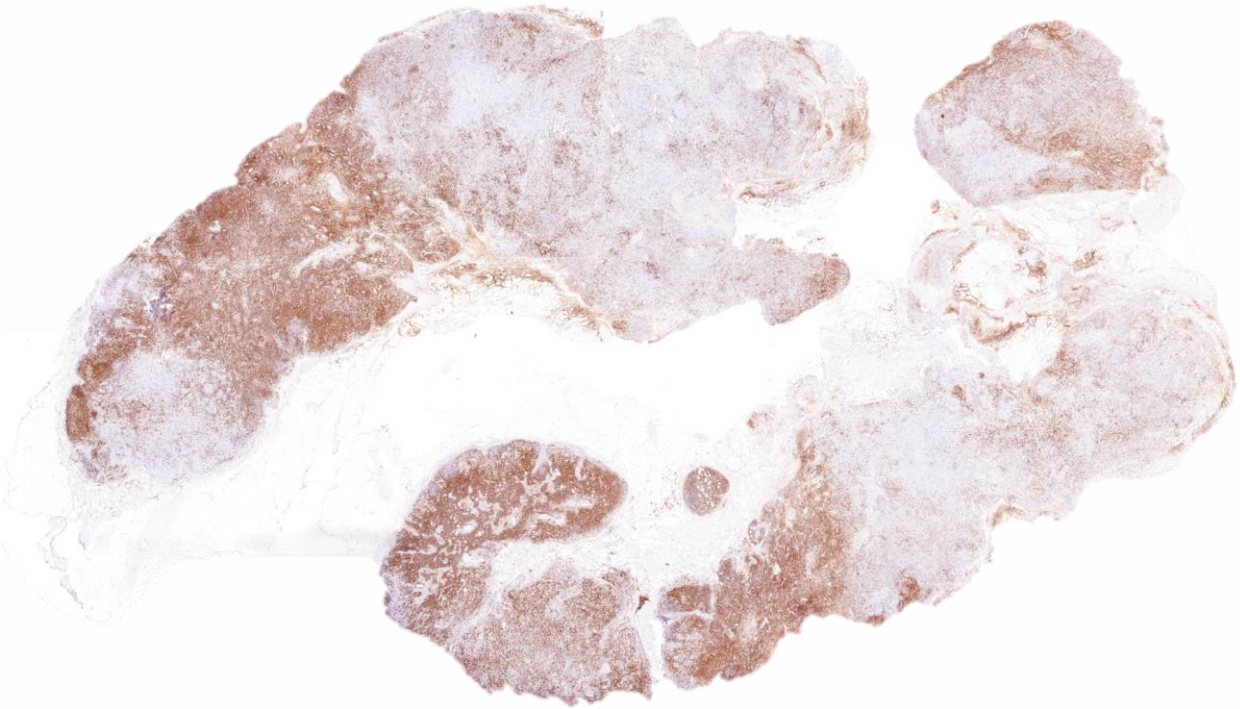




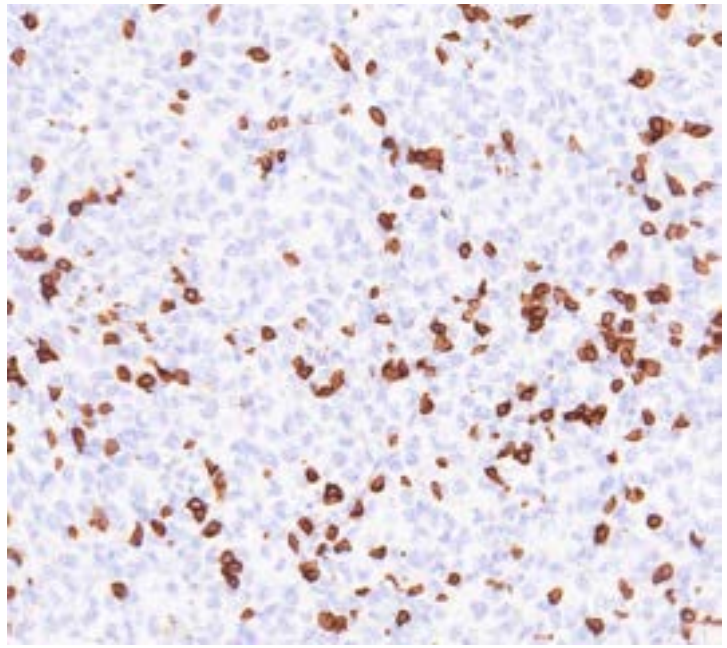
CD4

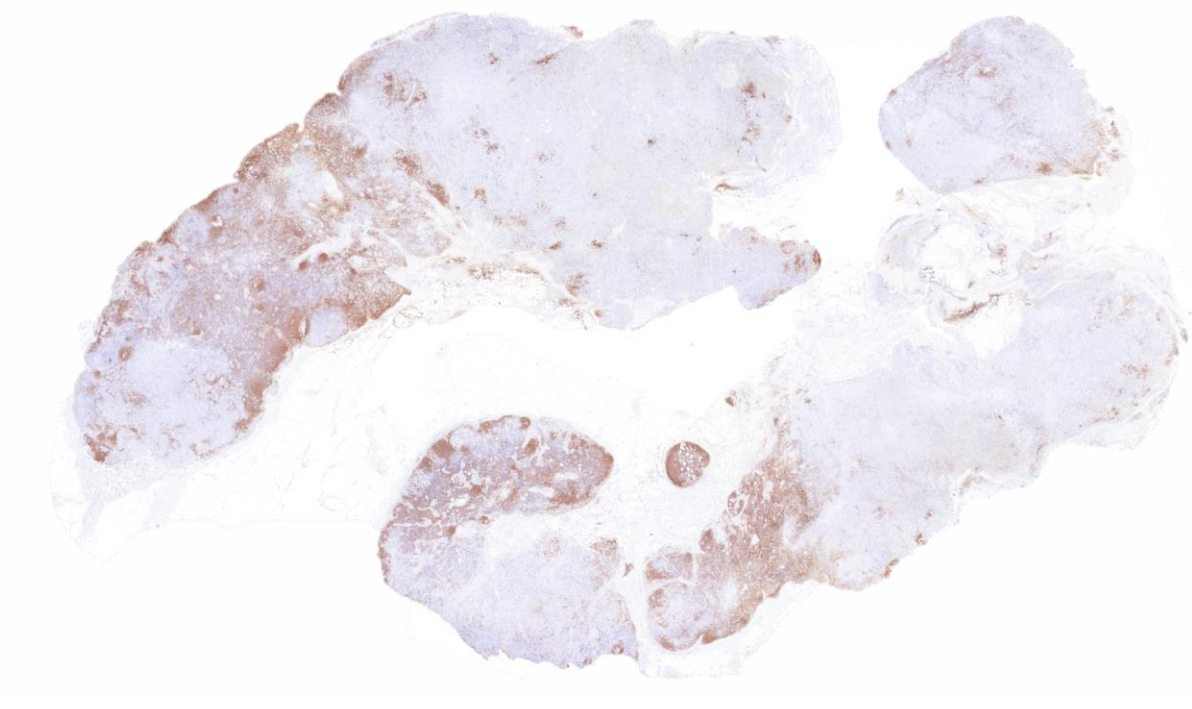


Differential diagnosis by provided IHC?

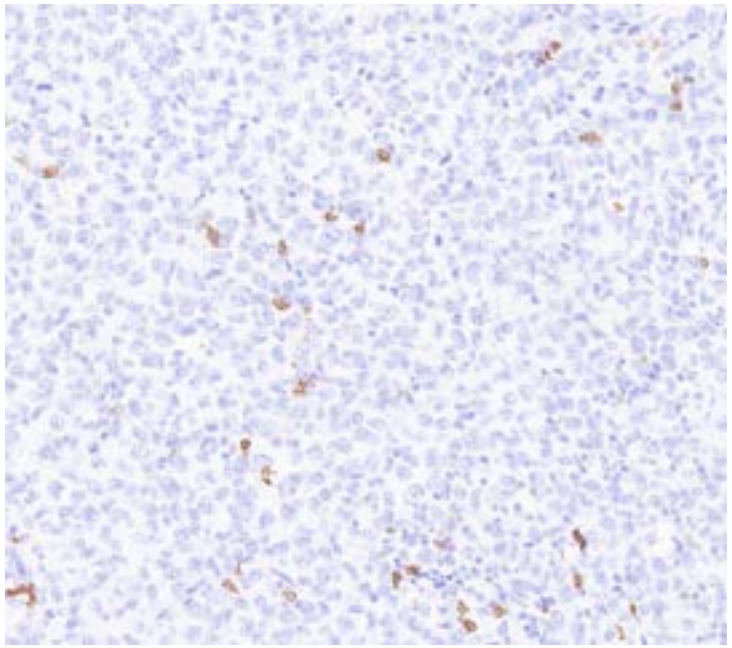


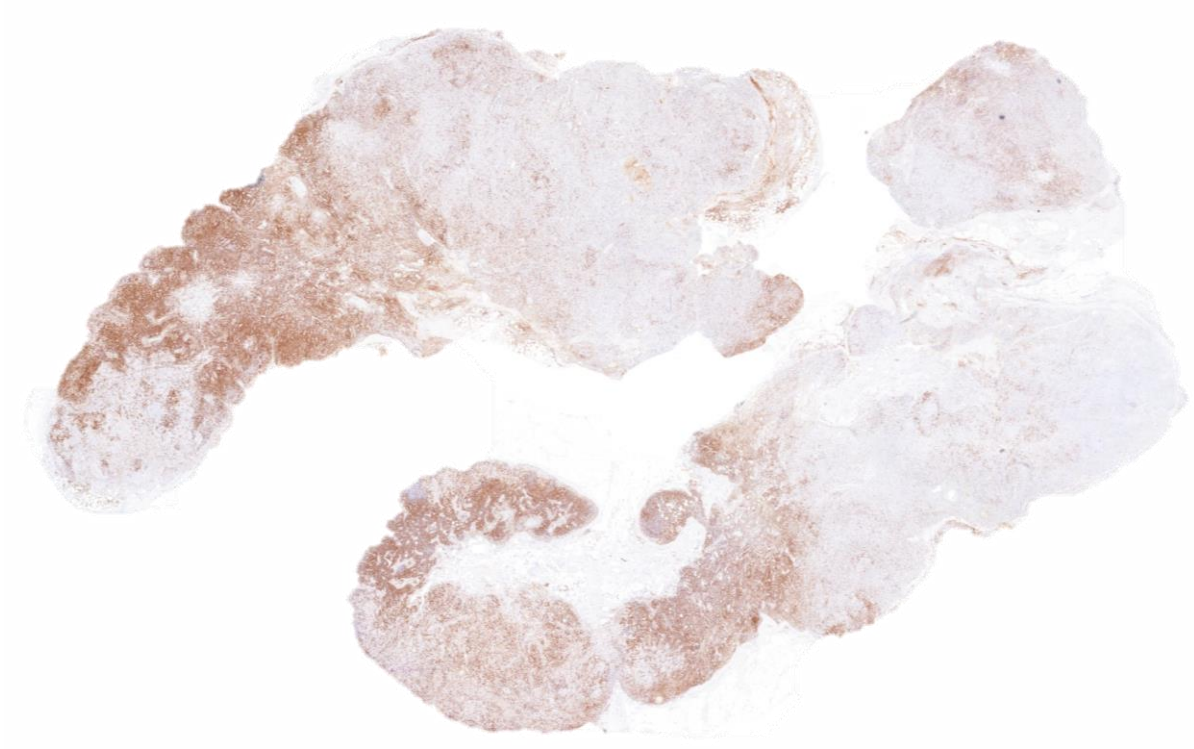
CD3



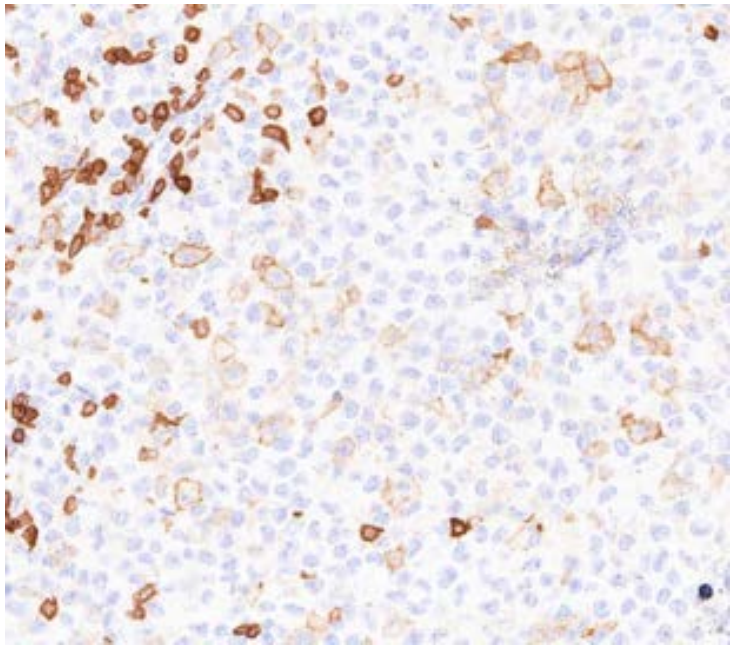


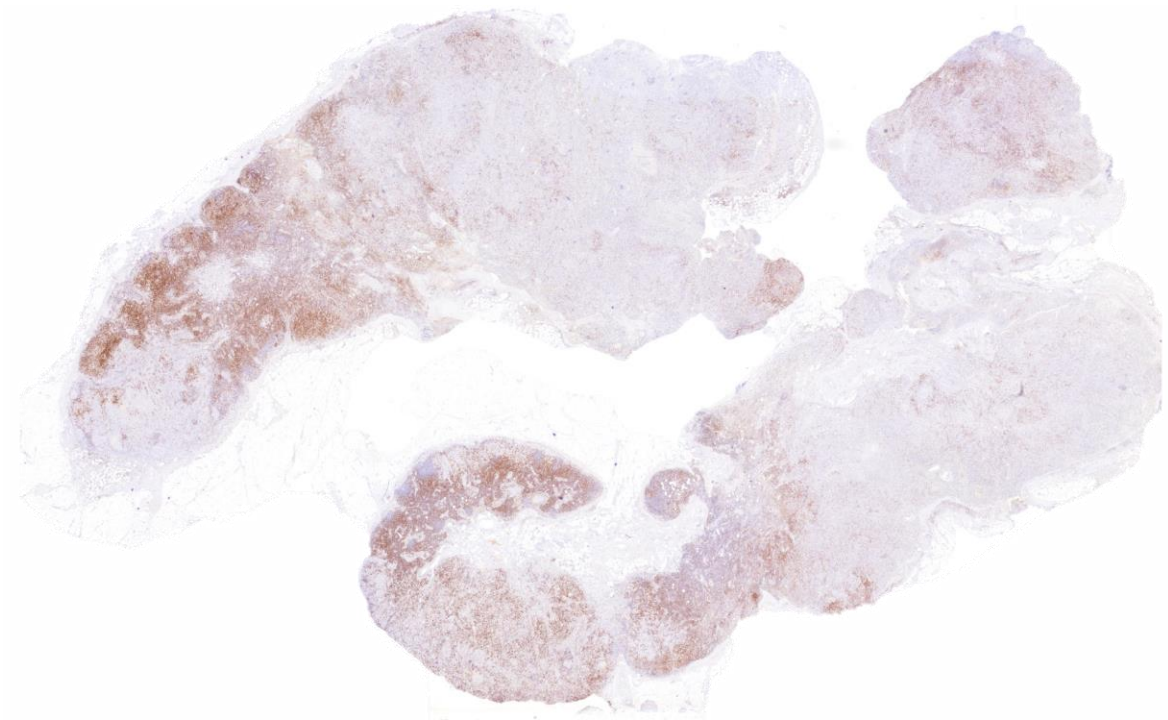
CD20



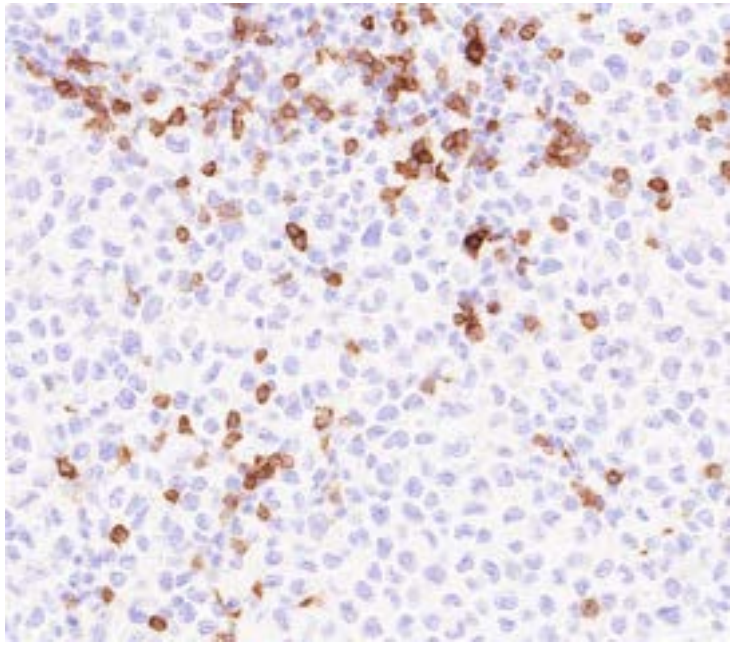


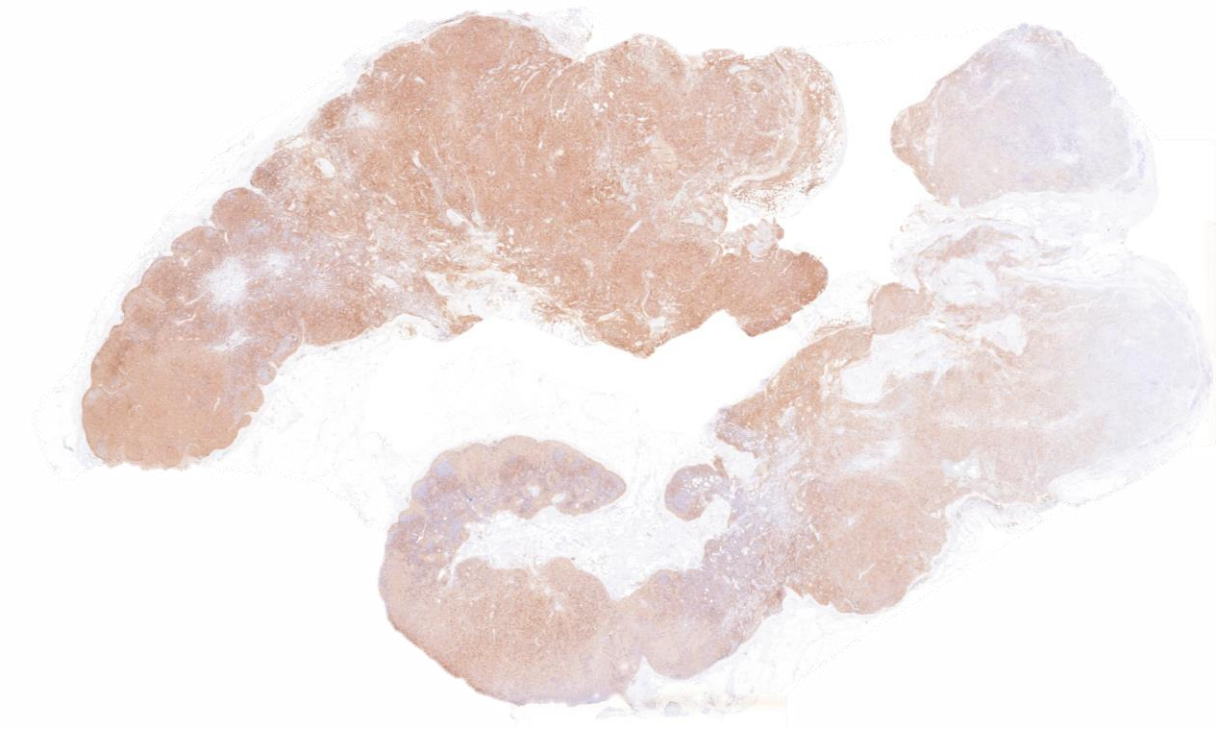
CD5



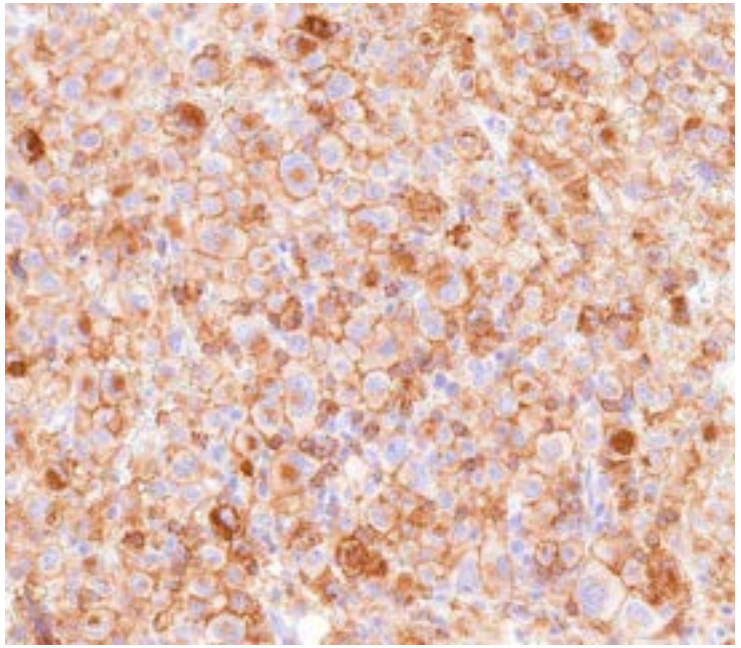


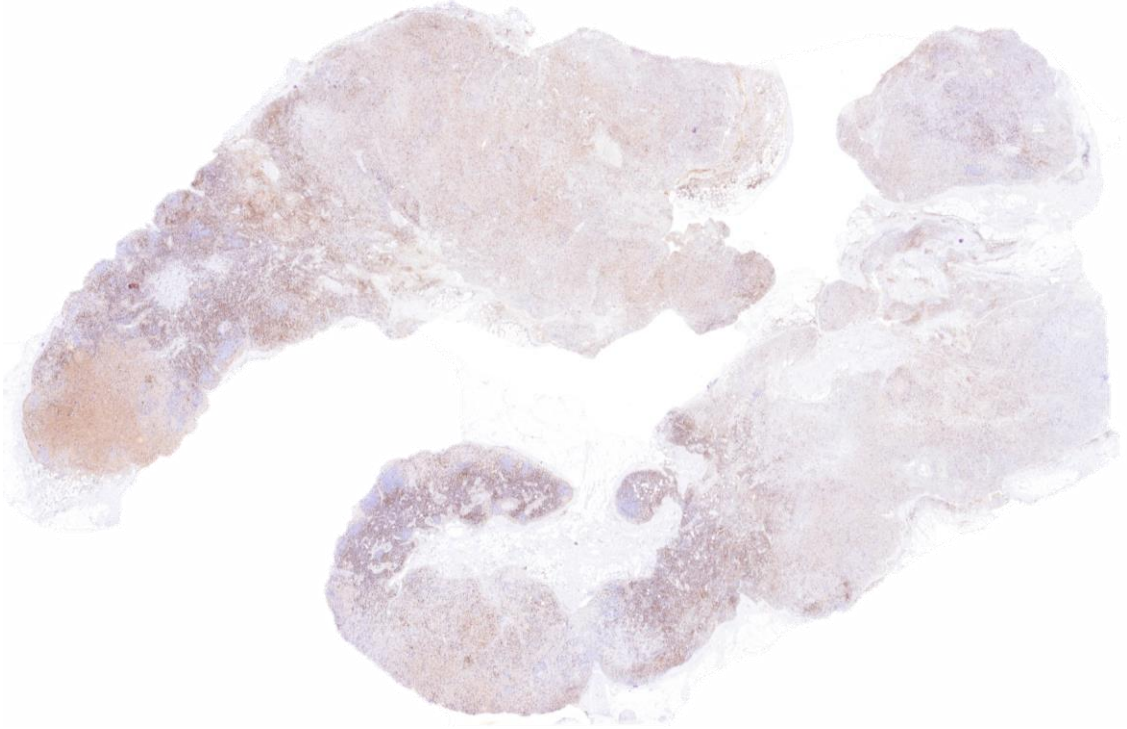
CD7



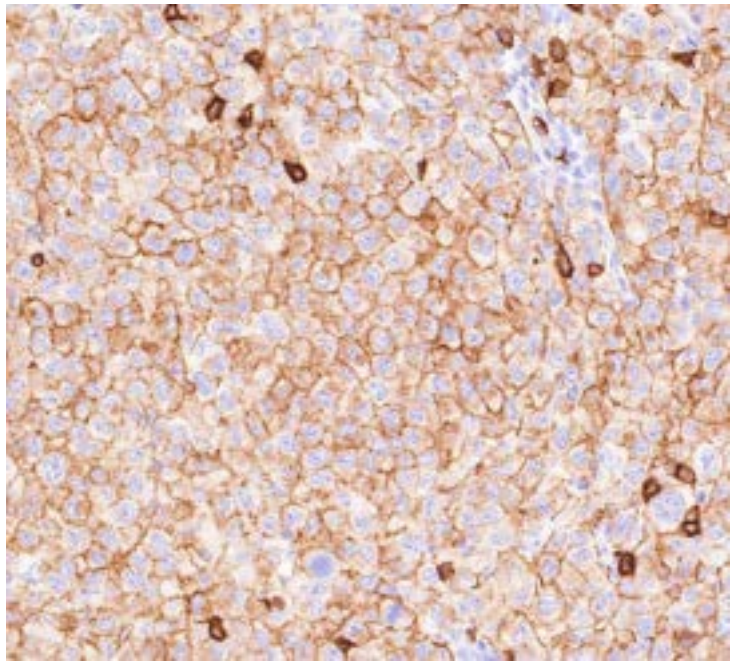


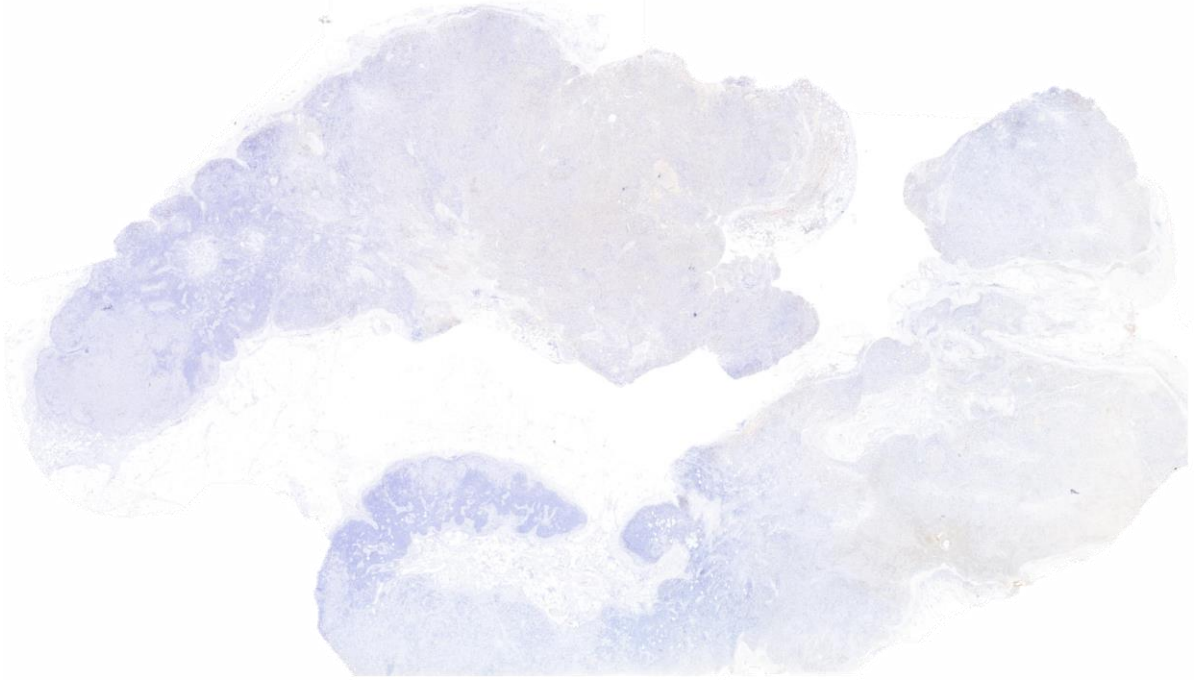
CD4



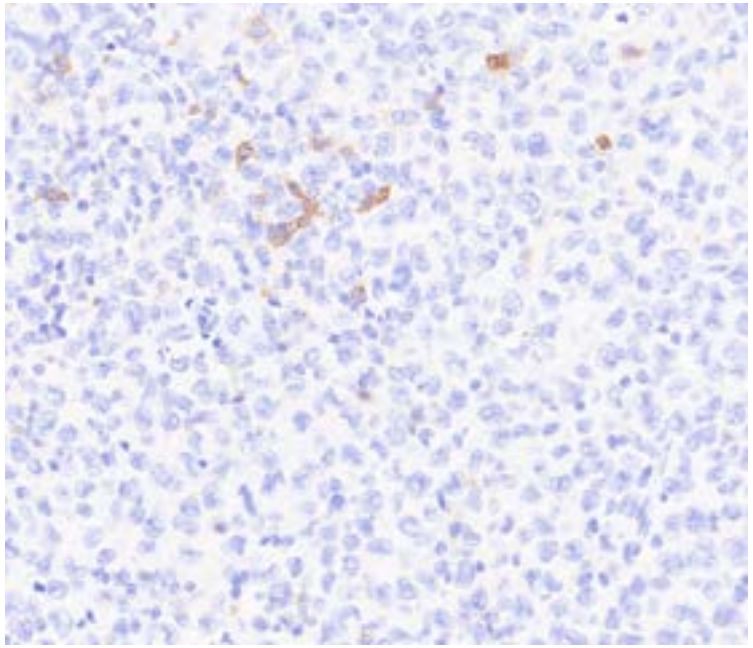


CD8

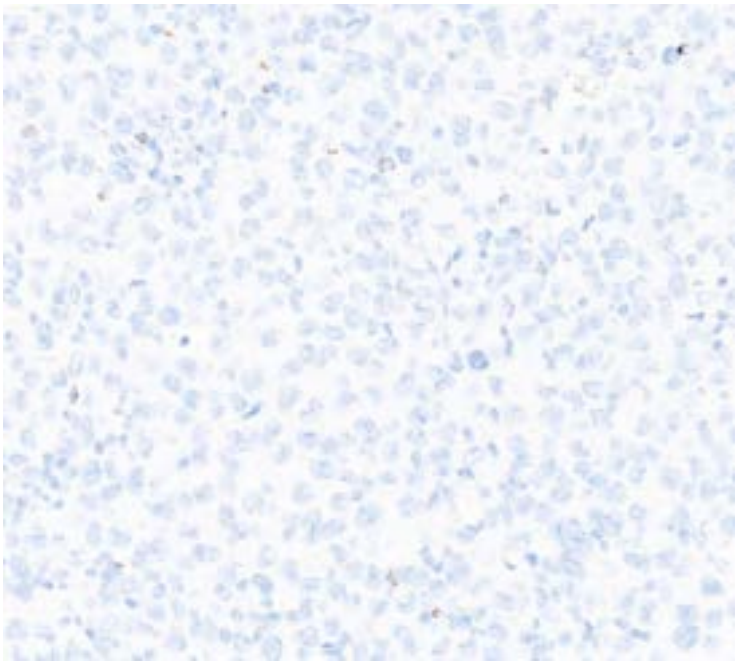


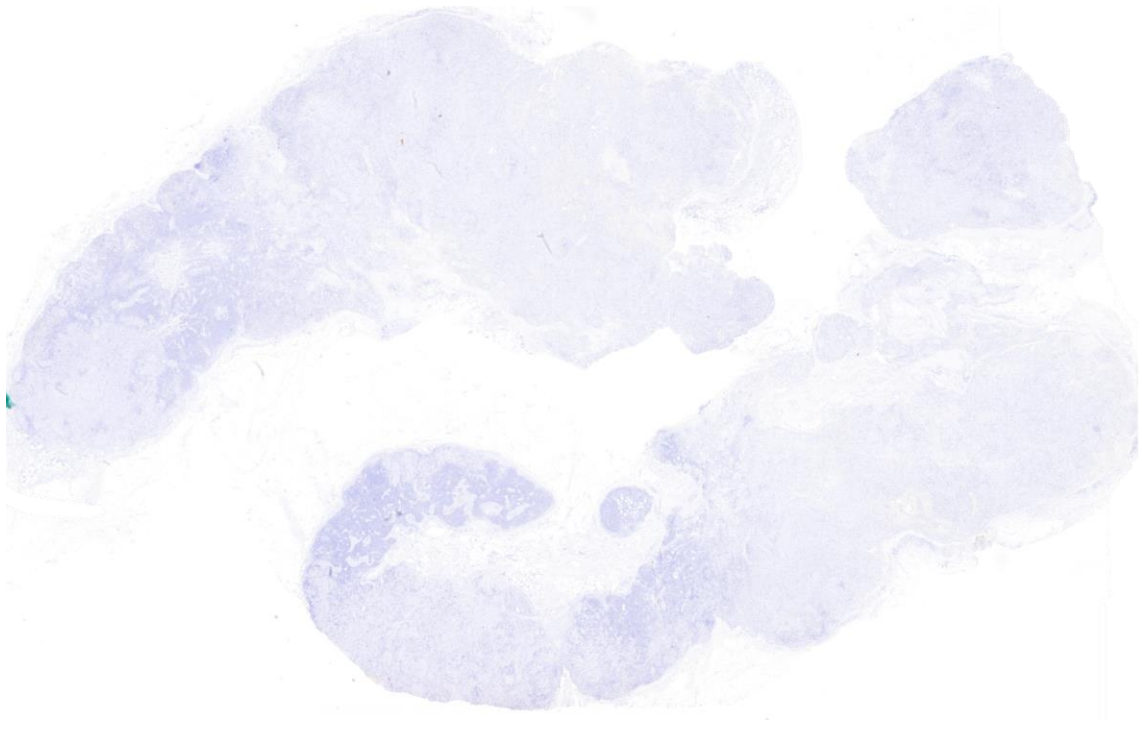


PD1

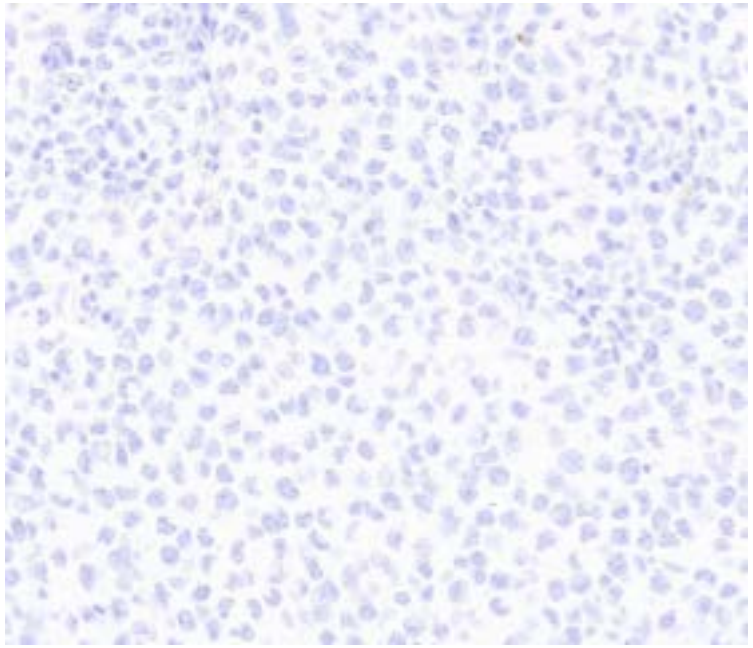


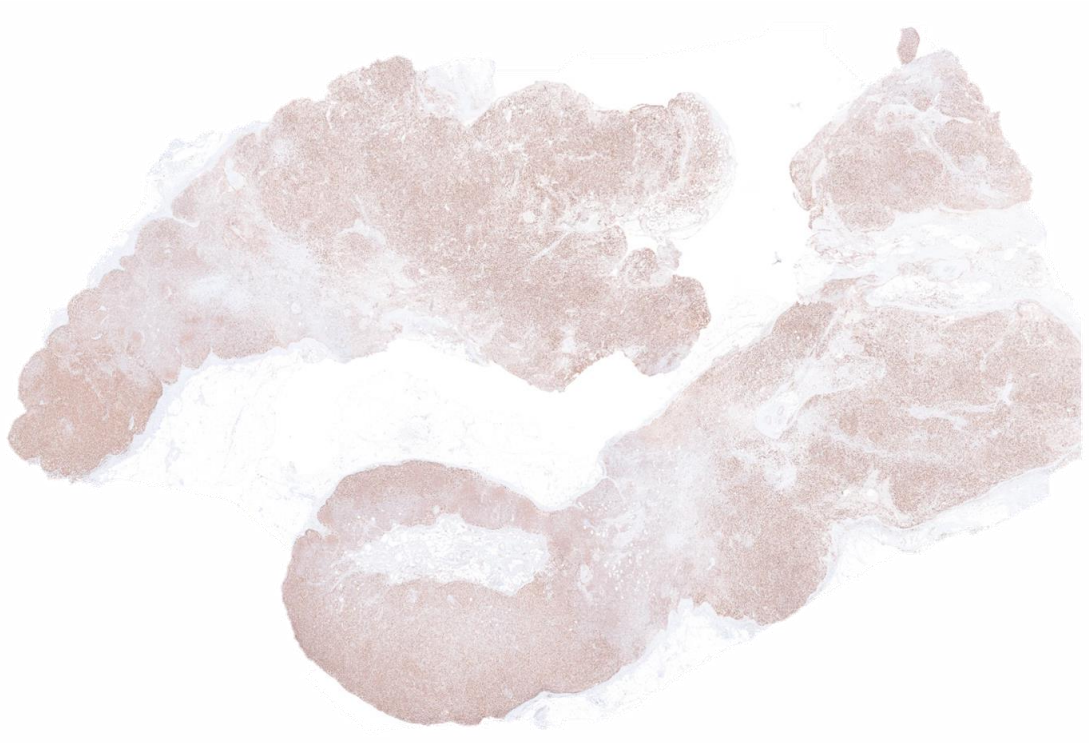
Granzyme B



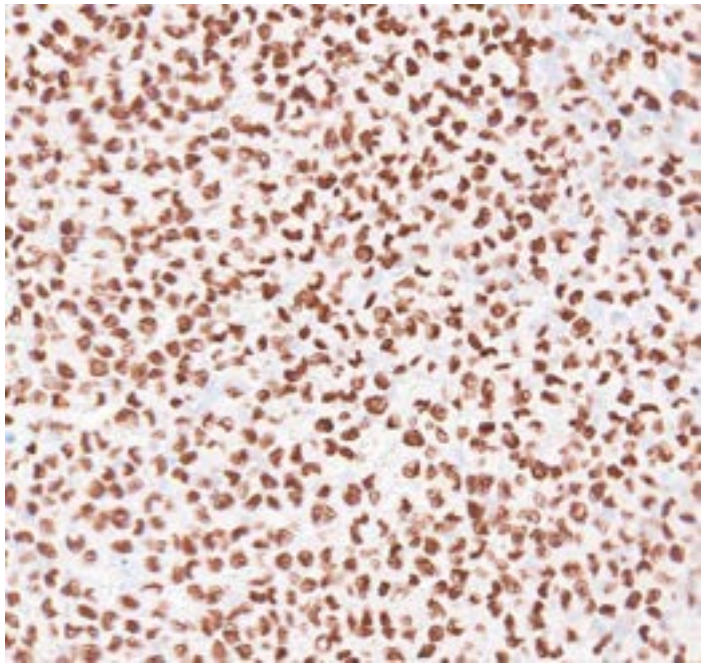


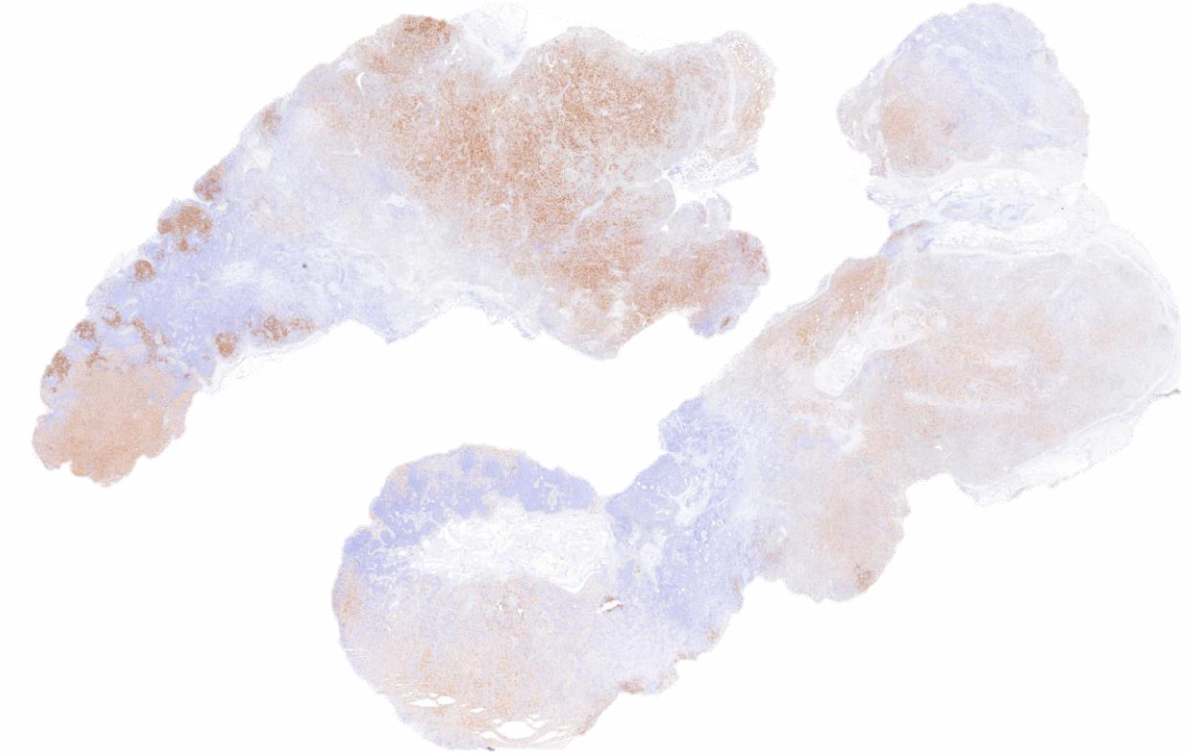
CD30



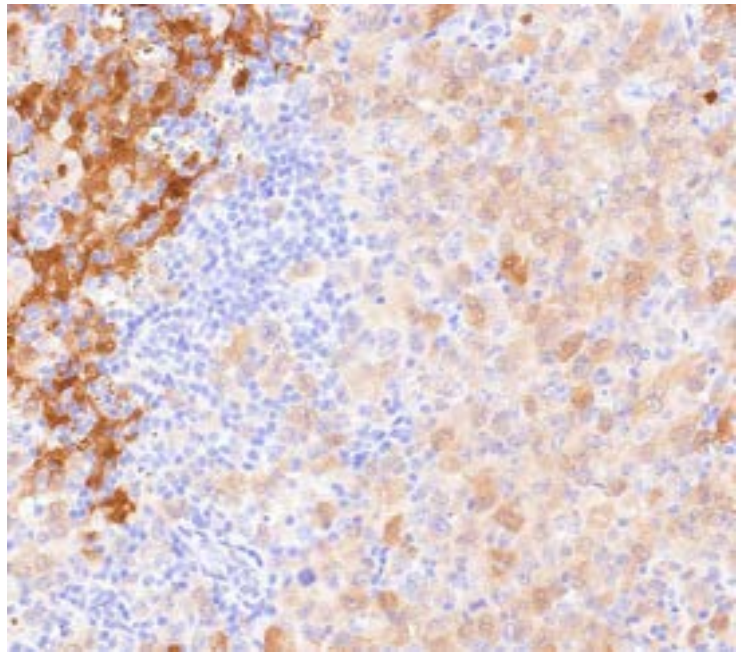


PU.1

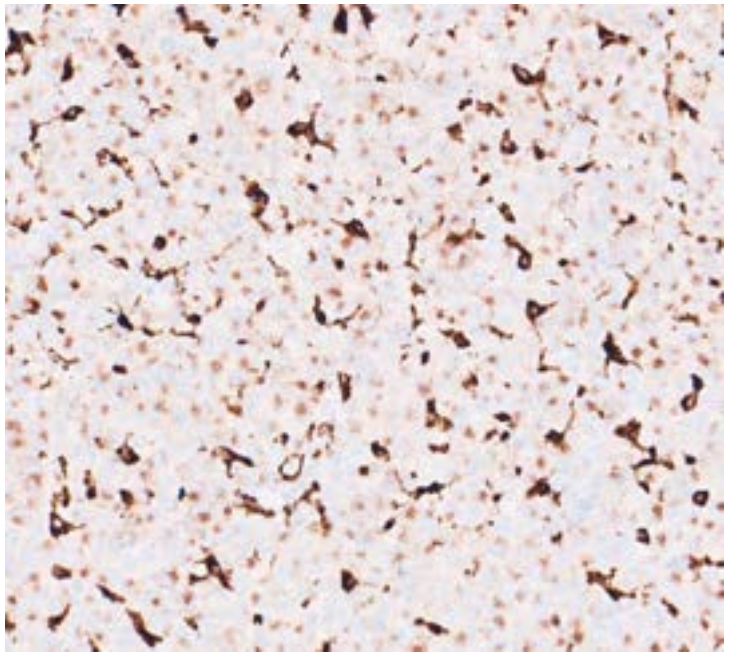


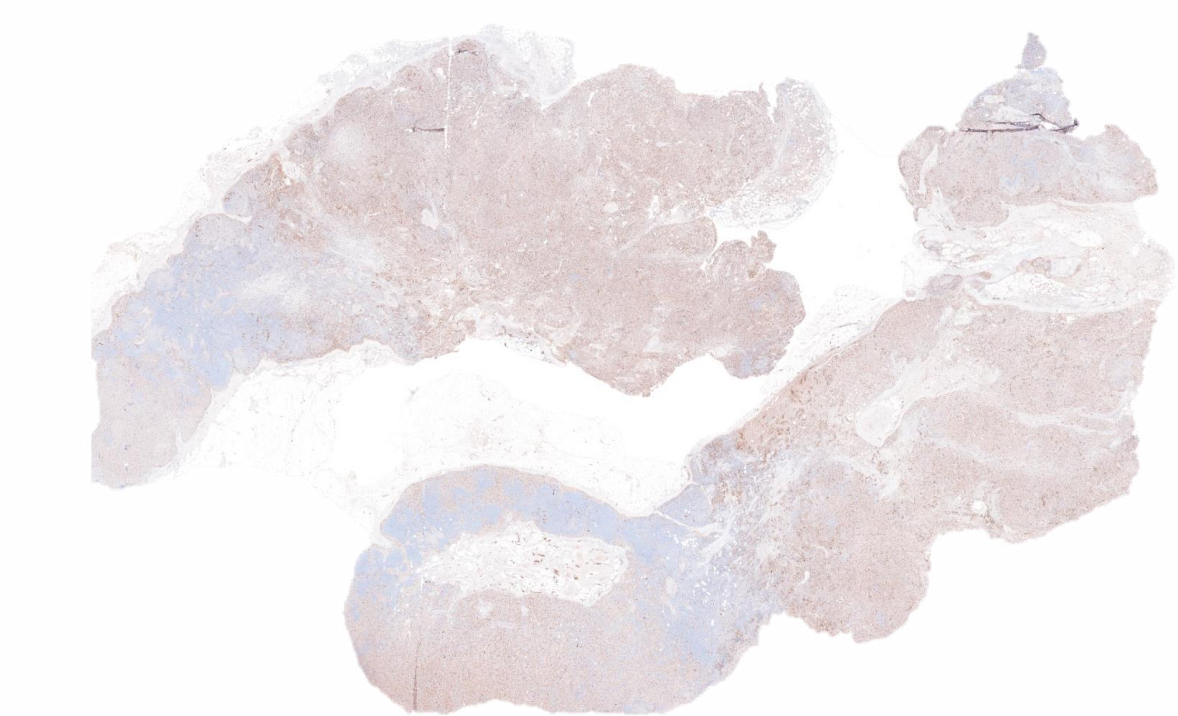


S100

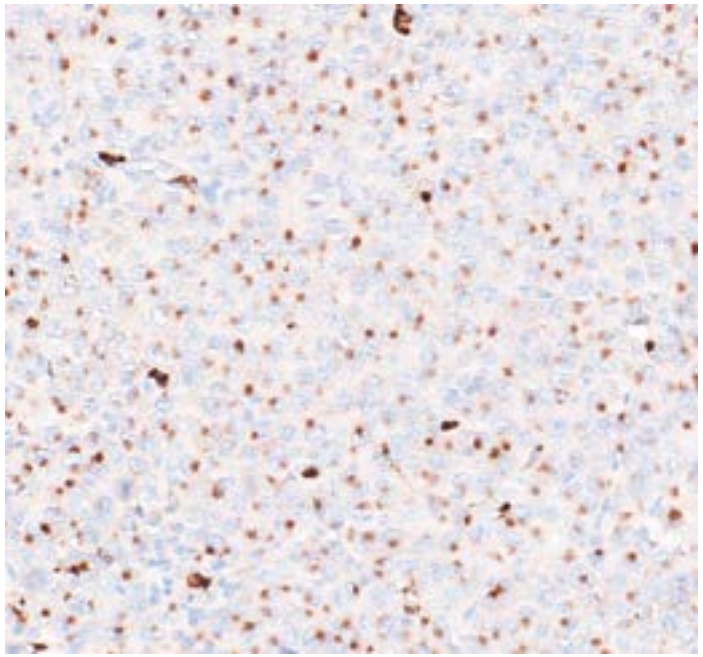


CD68
(PG-M1)

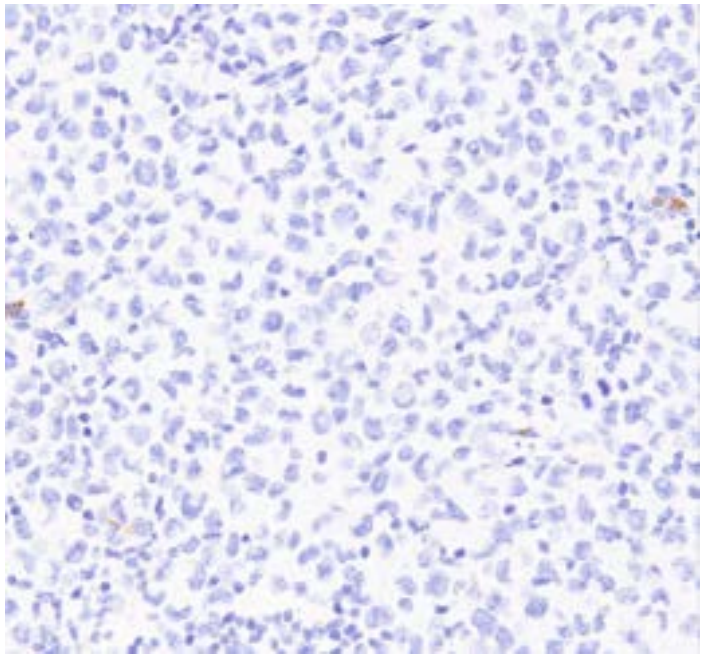


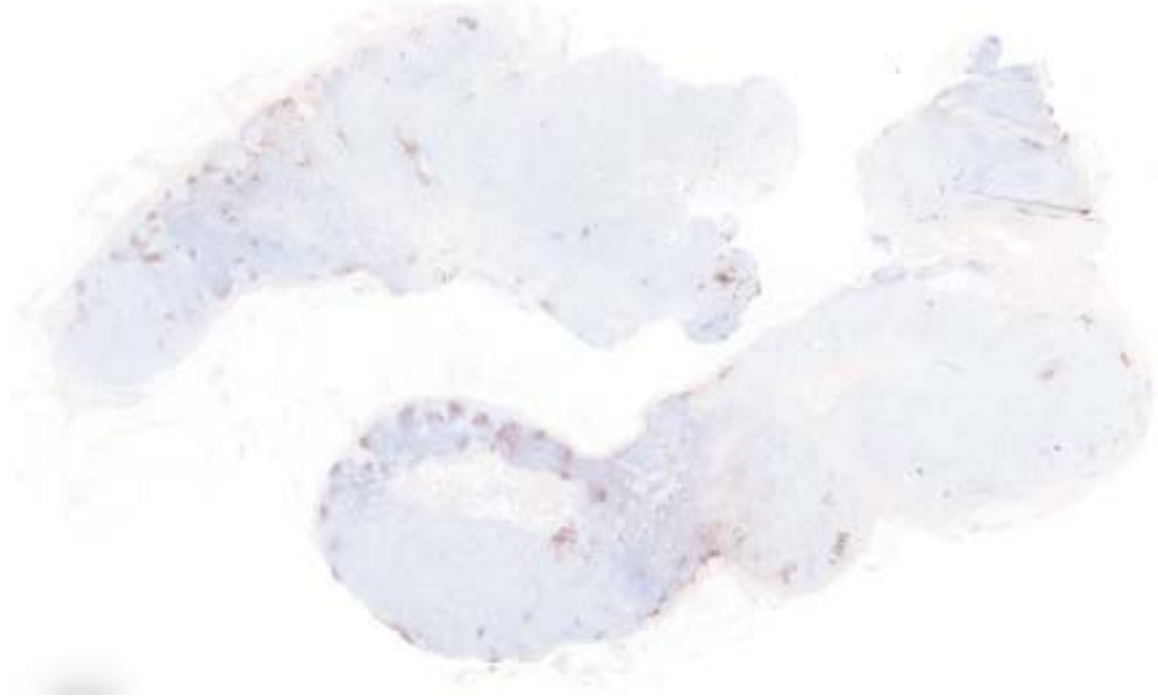


Muramidase (lysozyme)

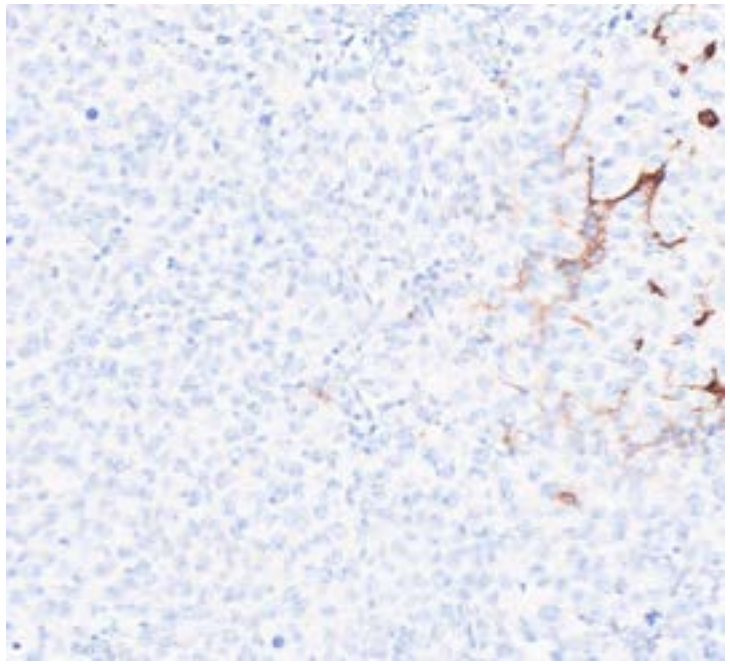


Myeloperoxidase

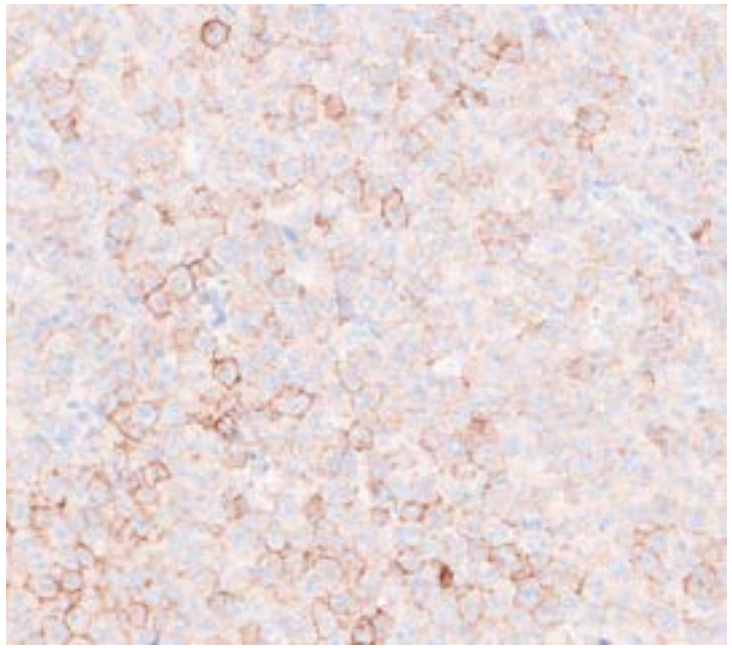


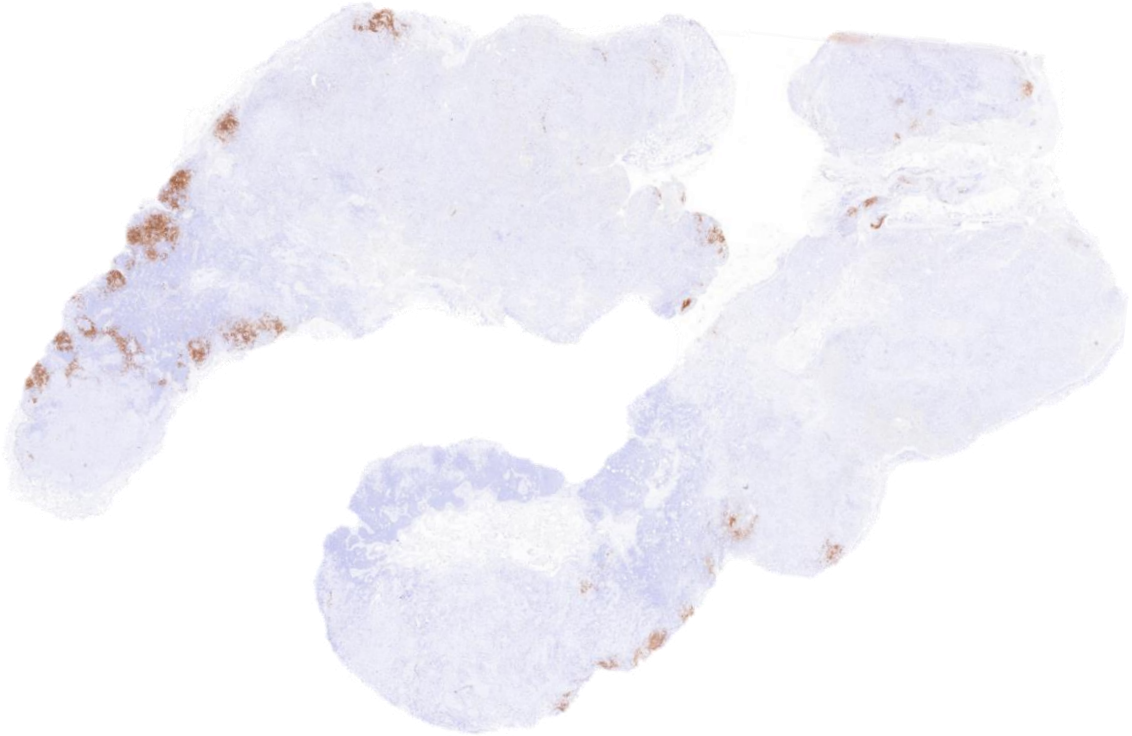


CD21

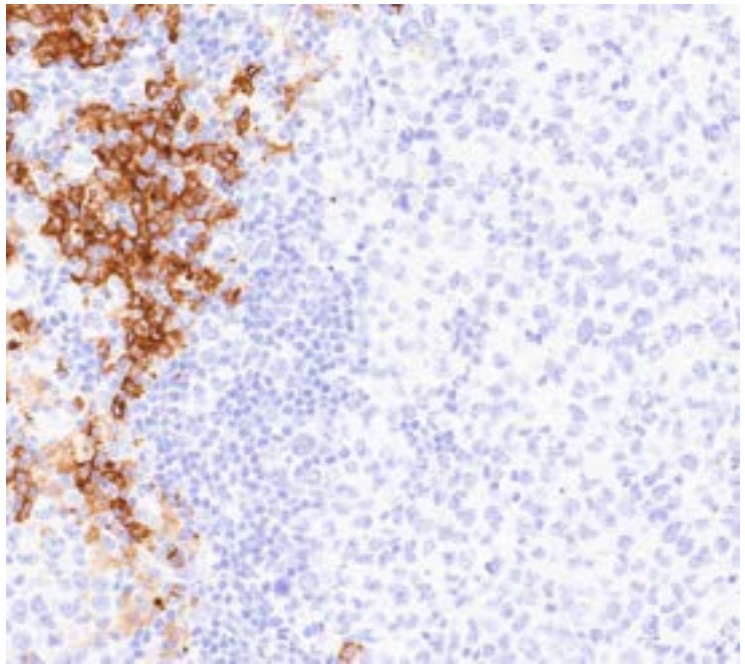


CD303

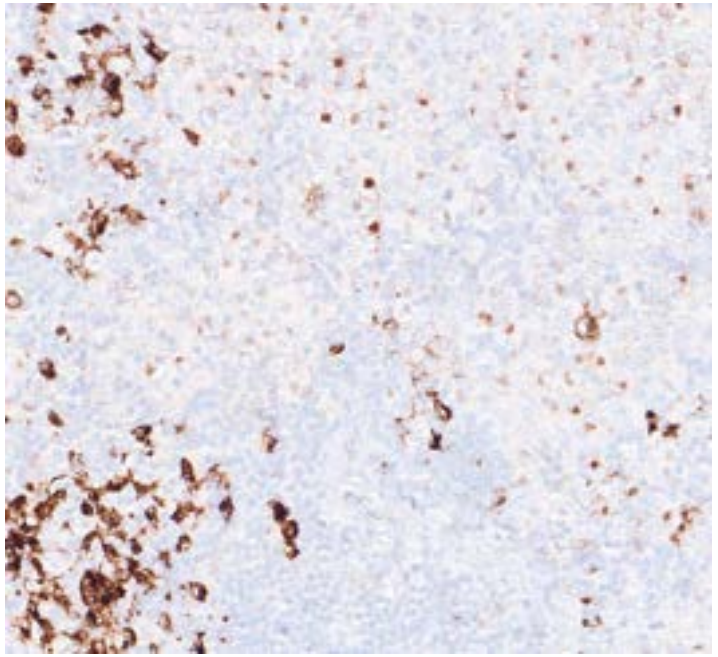


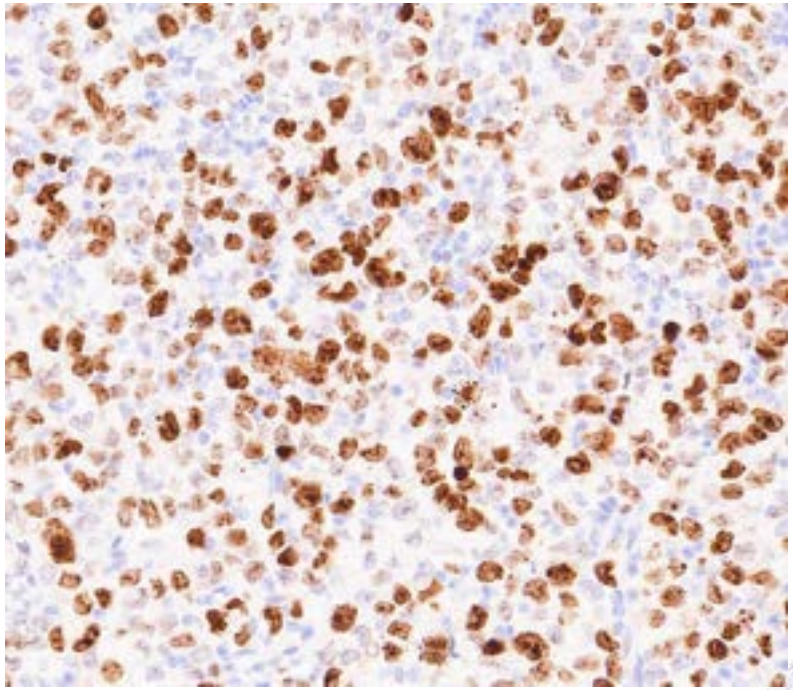


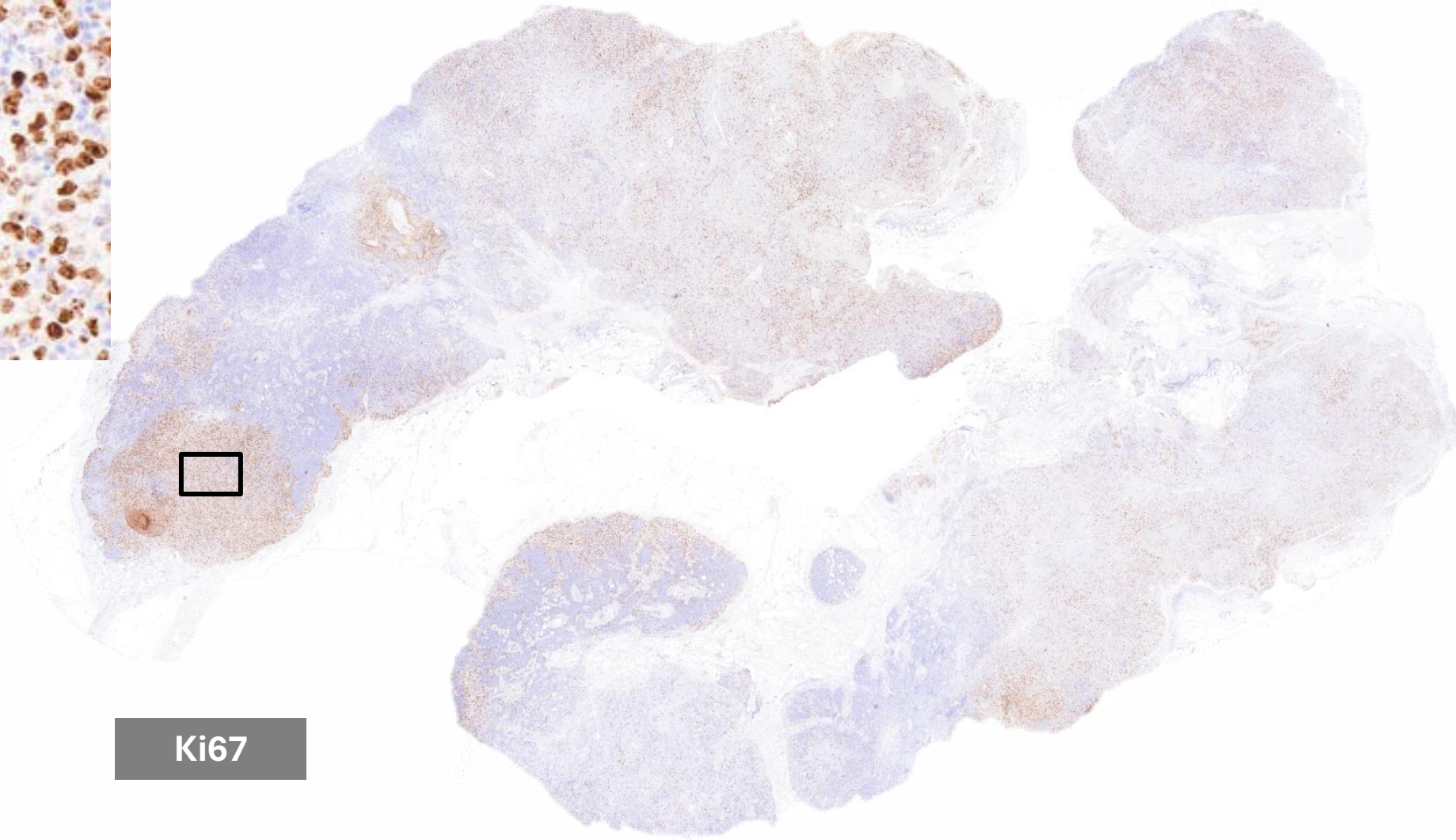
CD1a



Langerin (CD207)







Ki67

Immunohistochemical stain summary

Positive stains
CD45
CD4
CD5 (dim subset)
CD8 (dim subset)
Cyclin D1
BCL6
S100
CD68 PGM1 (perinuclear/golgi pattern)
PU.1
IRF8
Muramidase (perinuclear/golgi pattern)
Langerin (perinuclear/golgi pattern)
CD303 (subset)

Negative stains	
CD2	**ALK 1**
CD3	**CD30**
CD7	**CD15**
CD56	**E-cadherin**
Granzyme B	**CD117**
TIA-1	**Myeloperoxidase**
Perforin	**BRAF V600E**
PD-1	**NRAS Q61R**
CD20	**Mutant NPM1**
PAX5	**P53** (wild type)
OCT3/4	**CD123**
MUM1	**CD1a**
CD10	**TCL1a**
BCL2	**CD21**
EBER-CISH	**CD23**
CK 8/18	**CD35**
CK AE1/AE3	

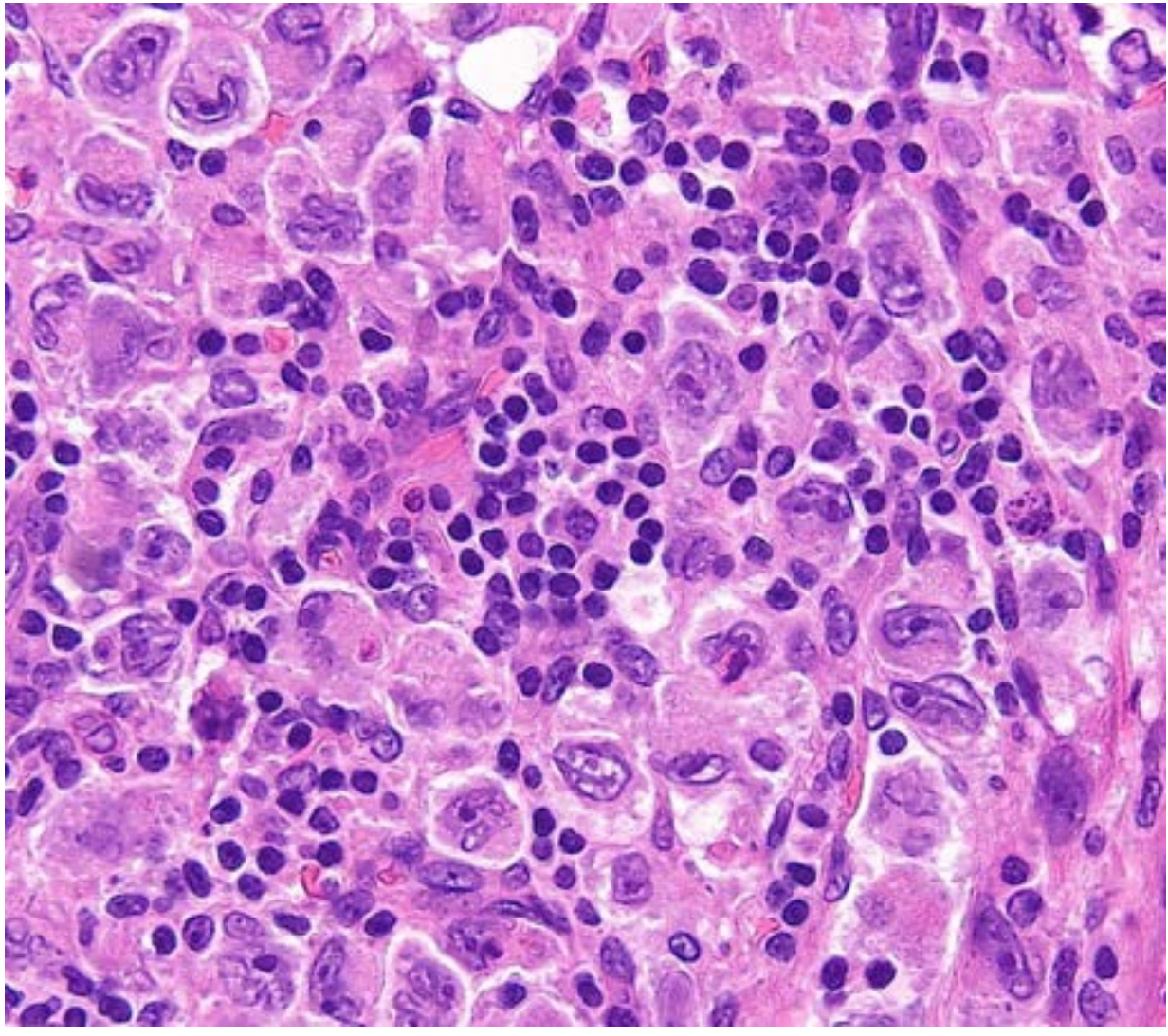
Ancillary studies

- Flow cytometry
  - No evidence of a monotypic B cell or aberrant T cell population
- Molecular / cytogenetic studies
  - Not performed (outside consult case)
- No patient follow up available (outside consult case)

Final Diagnosis?

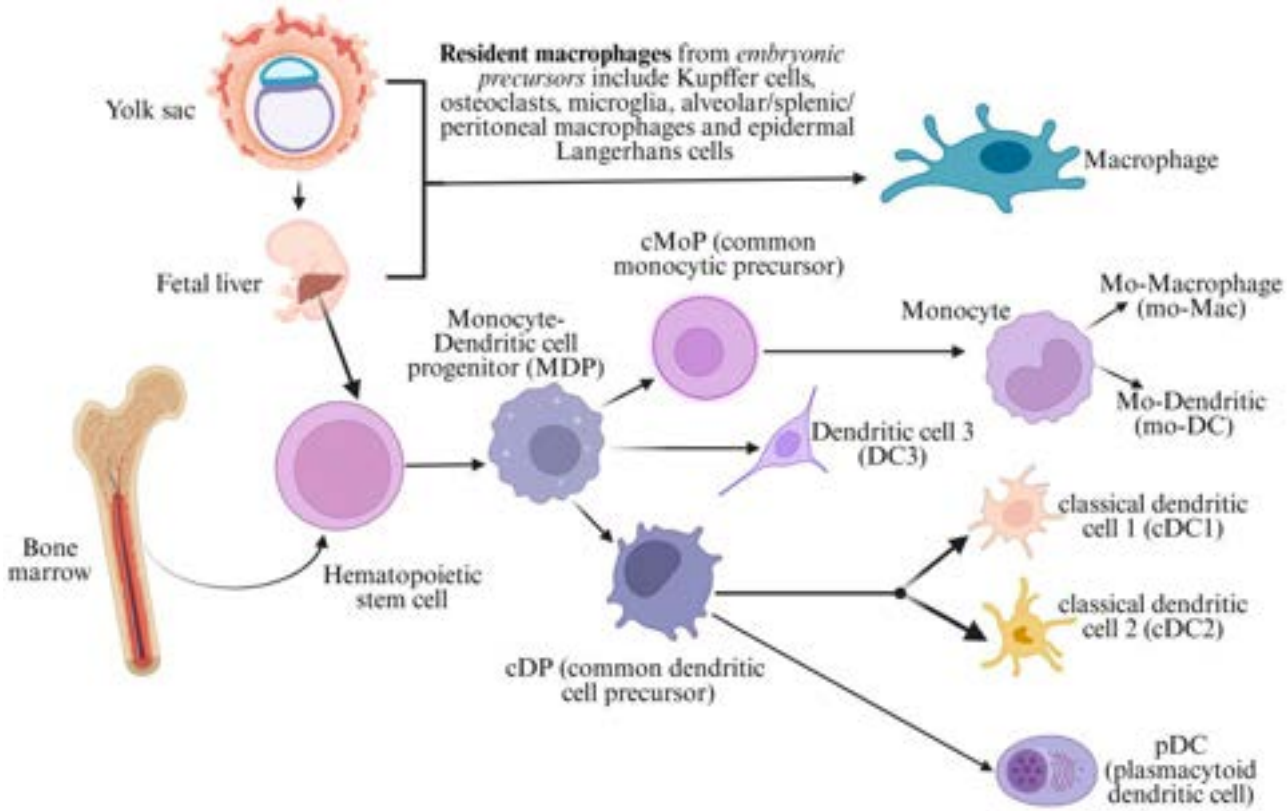
Final Diagnosis

Langerhans cell sarcoma



Overview – Langerhans Cells

- Mononuclear phagocytic system
  - Monocytes/macrophages
  - Dendritic cells



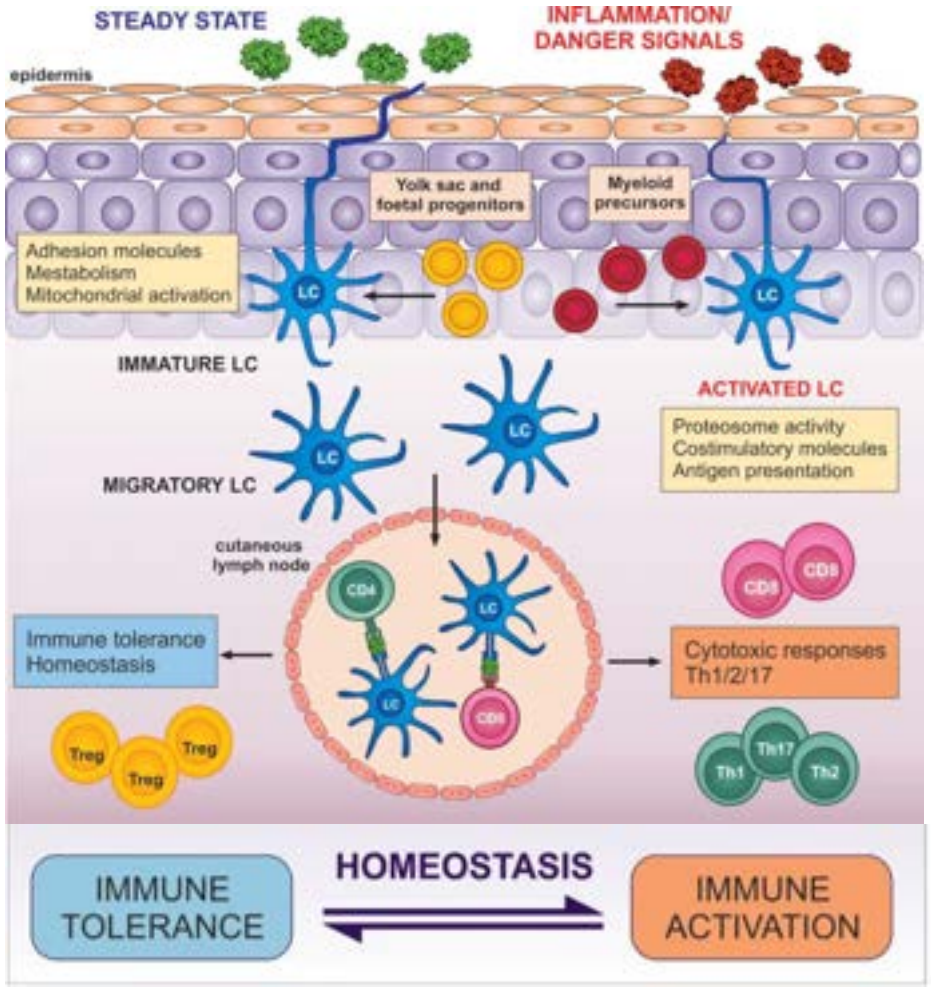
[image] Seth et al. *Cancers* 2025 PMID: 40563703

Overview – Langerhans Cells

- Mononuclear phagocytic system
  - Monocytes/macrophages
  - Dendritic cells

- Langerhans cells are a **specialized dendritic cell**
  - Found within the skin, gastrointestinal and respiratory epithelium/mucosa

- Langerhans cells are **antigen presenting cells (APCs)**
  - MHC Class II pathway, function in immune surveillance and regulation to process exogenous antigens and activate T cells



[image] Clayton et al. *Front Immunol* 2017 PMID: 29238347

Overview – Langerhans Cells

- Mononuclear phagocytic system
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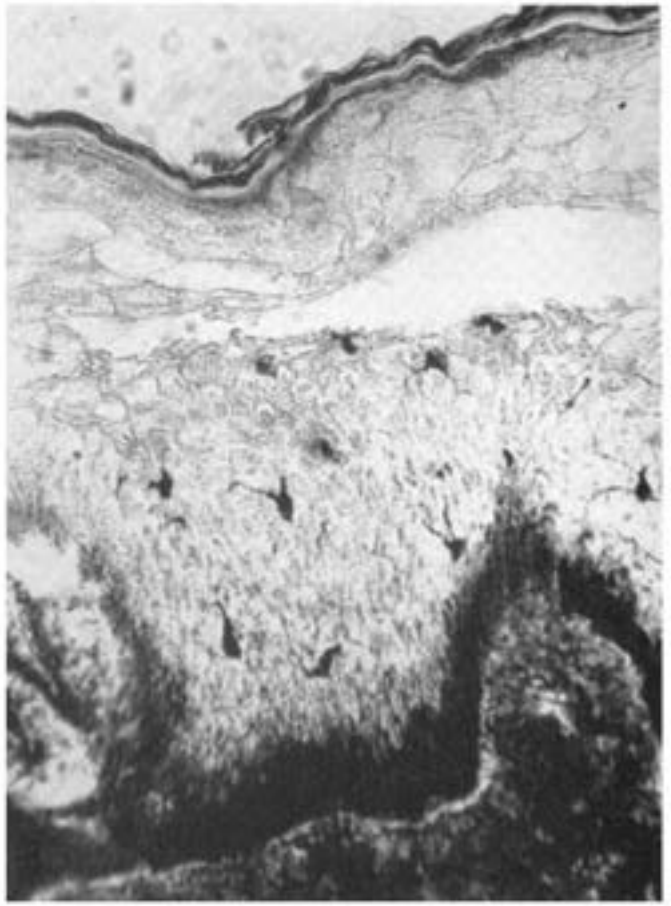
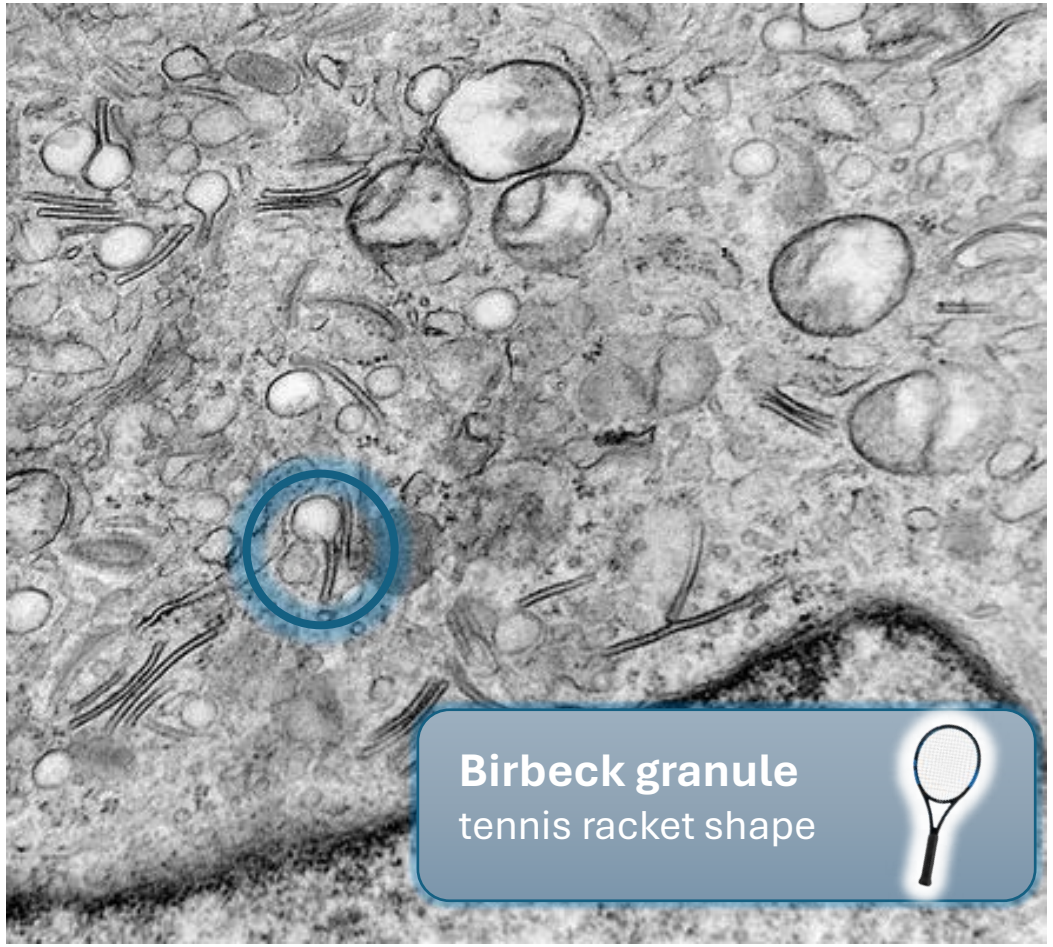
- Langerhans cells are a **specialized dendritic cell**
  - Found within the skin, gastrointestinal and respiratory epithelium/mucosa
- Langerhans cells are **antigen presenting cells (APCs)**
  - MHC Class II pathway, function in immune surveillance and regulation to process exogenous antigens and activate T cells
- Historical namesake
  - Discovered ~1800s by medical student Paul Langerhans
  - Used a gold staining technique and identified dendritic-shaped "nerve" cells in epidermis



Katz *Arch Dematol* 1980 PMID: 6779713; [image] Birbeck et al. *J. Invest. Dermatol,* 1961

Overview – Langerhans Cells

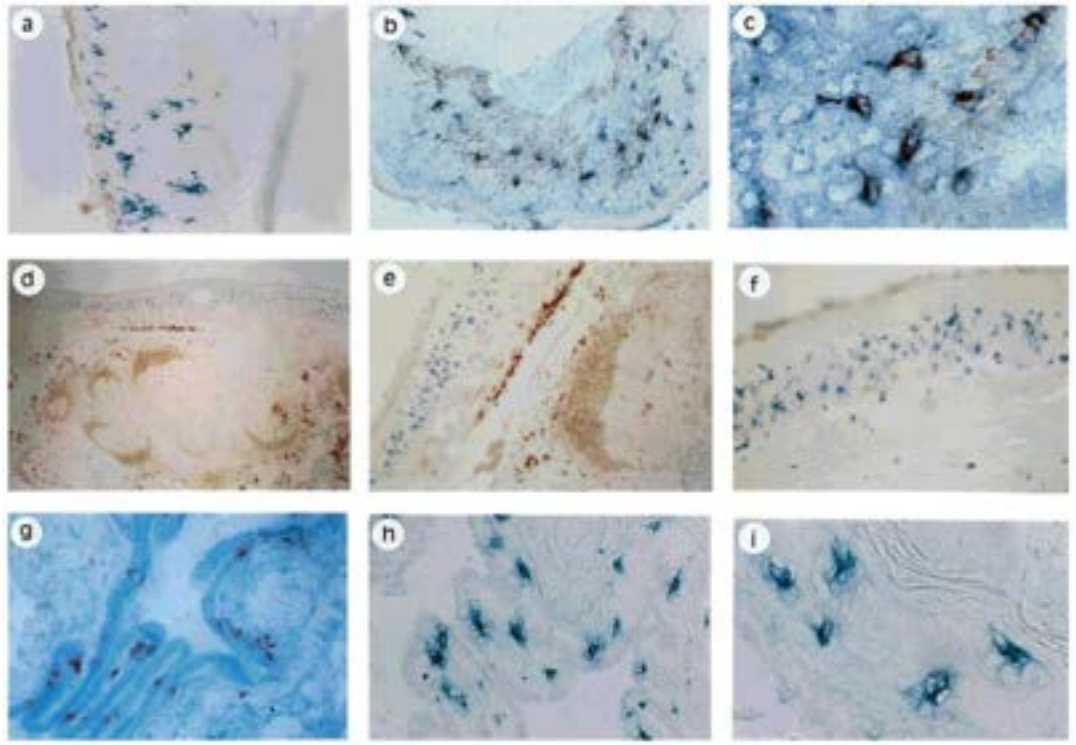
- Langerhans cells characterized by:
  - **Birbeck granules** = by electron microscopy
    - Discovered in ~1960s by transmission electron microscopist Michael Birbeck
    - Membrane bound cytoplasmic organelle



Valladeau et al. *Immunity* 2000 PMID: 10661407; [image] WebPathology Langerhans Cell Histiocytosis

Overview – Langerhans Cells

- Langerhans cells characterized by:
  - **Birbeck granules** = by electron microscopy
    - Discovered in ~1960s by transmission electron microscopist Michael Birbeck
    - Membrane bound cytoplasmic organelle
  - **Langerin (CD207)** = immunohistochemical stain
    - Transmembrane protein, endocytic lectin receptor
    - Binds antigens and induces formation of Birbeck granules to process antigens

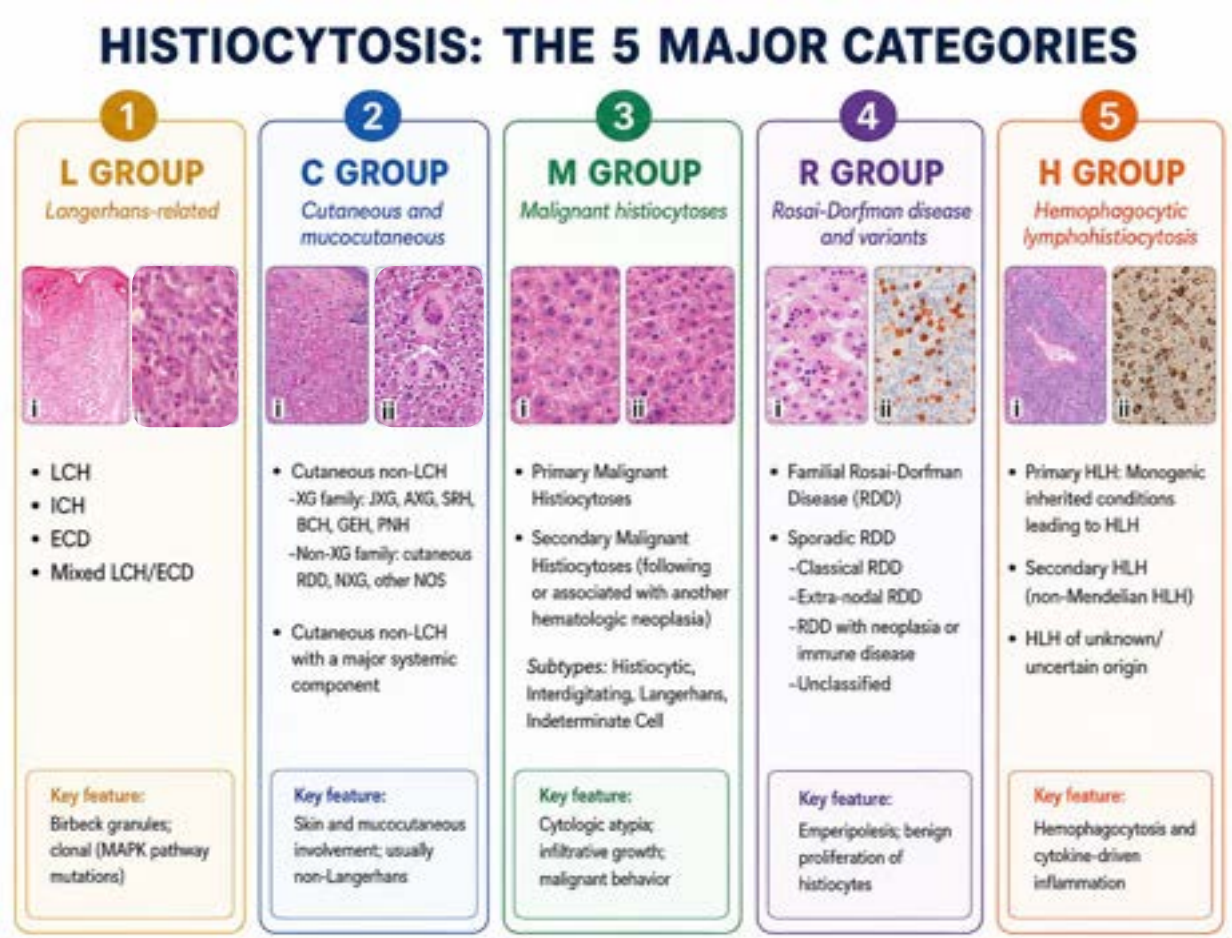


Valladeau et al. *Immunity* 2000 PMID: 10661407; [Image] Valladeau et al. *Eur J Immunol.* 1999 PMID: 10508244;

Overview – Disease classification

- Working group of the histiocyte society proposed the classification of histiocytoses

- **“M” group: malignant histiocytosis**
  - Defined by aggressive anaplastic features
  - In 2016, introduced subclassification
    - IHC phenotype
    - Primary vs. secondary



Emile et al. *Blood* 2016 PMID: 26966089 ; [image] ChatGPT generated adapted from Emile et al. *Blood* 2016

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    - Primary vs. secondary

- **Langerhans cell sarcoma (LCS)**
  - “M group” malignant histiocytoses
  - First recognized in 2001 WHO 3rd ed
  - Maintained in current WHO 5th ed and ICC

WHO Classification of Tumours Haematolymphoid tumours 5th ed; 2022 International Consensus Classification (ICC)

Overview – Disease classification

Evolution of the classification of “histiocytic/dendritic cell neoplasms”

- In previous WHO editions, follicular dendritic cell sarcoma (FDCS) was included within the category of “histiocytic/dendritic cell neoplasms”

- New WHO 5th ed, **FDCS now under “stroma-derived neoplasms” given distinct cell origin**

Table 1. Distinction in classifications of mesenchymal dendritic cell neoplasms versus histiocytic and classical dendritic/Langerhans cell and plasmacytoid dendritic cell neoplasms: comparisons of the WHO (revised fourth edition and fifth edition) and ICC classifications of hematopoietic tumors.

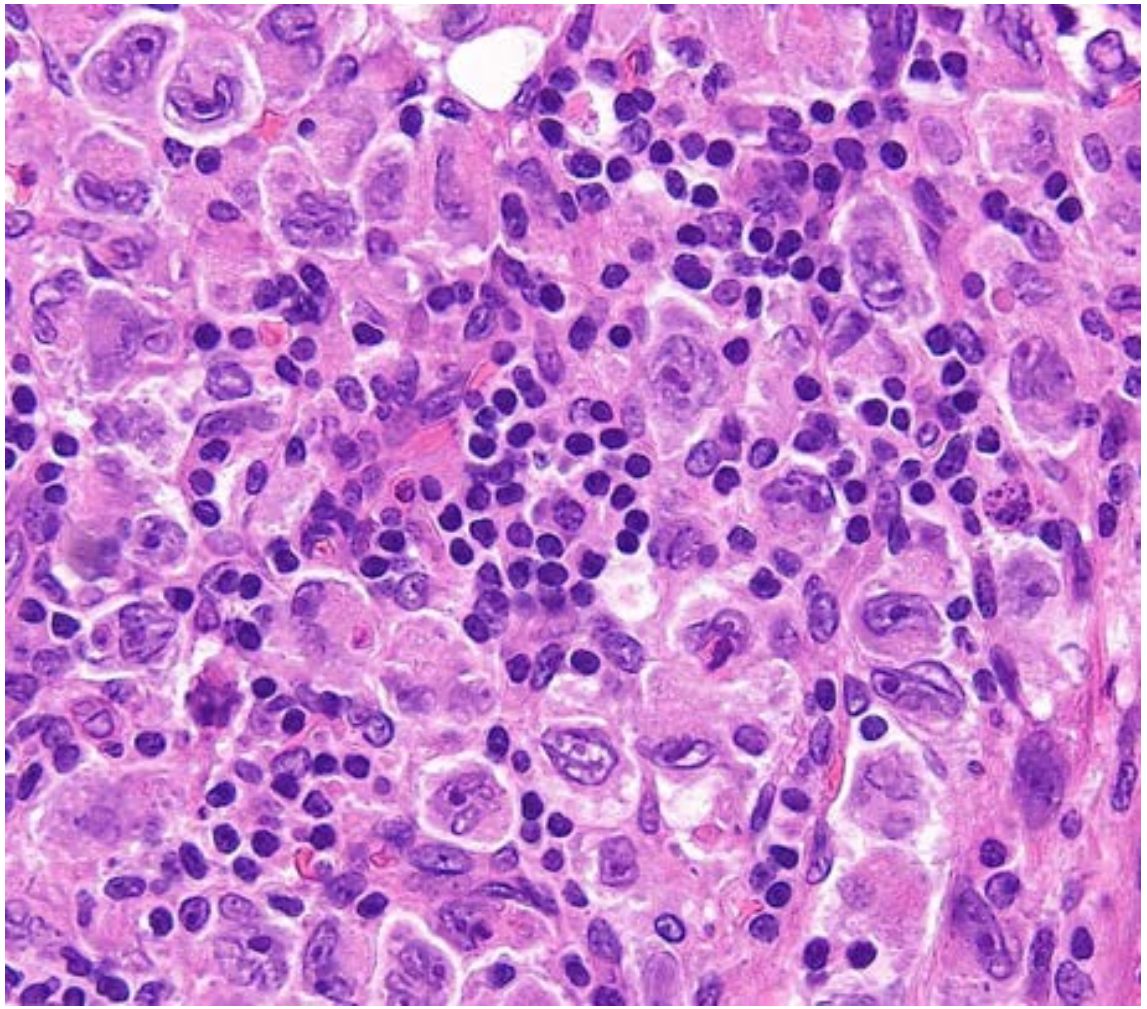
WHO (Revised Fourth Edition, 2016)	WHO (Fifth Edition, 2022)	ICC (2022)
	Mesenchymal Dendritic Cell Neoplasms	
	Follicular dendritic cell sarcoma	Follicular dendritic cell sarcoma
	Fibroblastic reticular cell tumor	Fibroblastic reticular cell tumor
	EBV-positive inflammatory FDCS #	EBV-positive inflammatory FDCS/FRCT
Follicular dendritic cell sarcoma		
Fibroblastic reticular cell tumor	**Histiocytic/Dendritic Cell Neoplasms**	
Inflammatory pseudotumor-like follicular/fibroblastic dendritic cell sarcoma	Blastic plasmacytoid dendritic cell neoplasm	
	Mature plasmacytoid dendritic cell proliferation associated with myeloid neoplasm *	Langerhans cell histiocytosis
Langerhans cell histiocytosis	Langerhans cell histiocytosis	Langerhans cell sarcoma
Langerhans cell sarcoma	Langerhans cell sarcoma	Indeterminate dendritic cell histiocytosis
Indeterminate dendritic cell tumor	Indeterminate dendritic cell tumor	Interdigitating dendritic cell sarcoma
Interdigitating dendritic cell sarcoma	Interdigitating dendritic cell sarcoma	Erdheim–Chester disease
Erdheim–Chester disease	Erdheim–Chester disease	Disseminated JXG
Disseminated JXG	JXG	Histiocytic sarcoma
Histiocytic sarcoma	Histiocytic sarcoma	Rosai–Dorfman disease *
	Rosai–Dorfman disease *	ALK-positive histiocytosis *
	ALK-positive histiocytosis *	

WHO (fifth edition) classification indicates fibroblastic reticular cell differentiation in EBV-positive mesenchymal dendritic cell neoplasms with lack of FDC markers, although it does not indicate EBV-positive FRCT as a distinct subtype but rather subclassifies within the category of EBV-positive inflammatory FDCS. * Newly recognized distinct neoplasms. Abbreviations: FDCS: follicular dendritic cell sarcoma; FRCT: fibroblastic reticular cell tumor; JXG: juvenile xanthogranuloma; WHO: World Health Organization; ICC: International Consensus Classification.

[image] Seth et al. *Cancers* 2025 PMID: 40563703

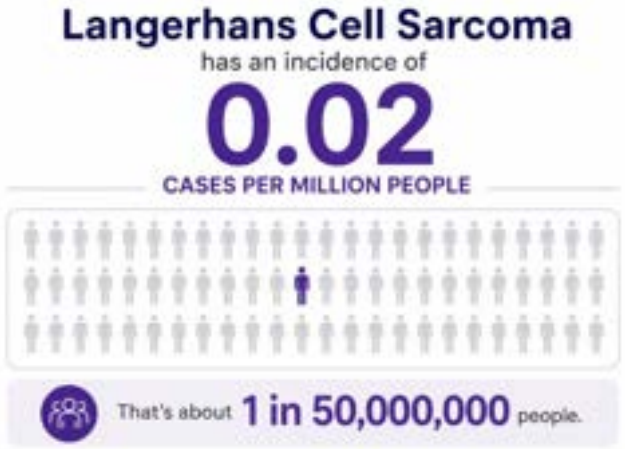
Langerhans cell sarcoma (LCS)

- Malignant neoplasm
- Aggressive behavior
- Anaplastic cytology
- Langerhans cell phenotype
  - Langerin (CD207) by IHC stain
  - Birbeck granules by electron microscopy



Epidemiology & Clinical features

- Epidemiology
  - **Very rare** (SEER: incidence 0.02 cases/million)
  - Adults, median 62 years, range 19-90 years
  - Slight male predominance



Harsha Tella et al. *Clin Lymphoma Myeloma Leuk* 2019 PMID: 31005630; WHO Classification of Tumours Haematolymphoid tumours 5th ed; [Image] ChatGPT generated

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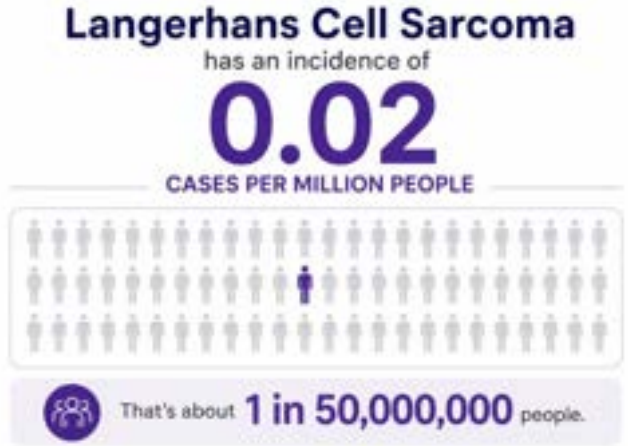
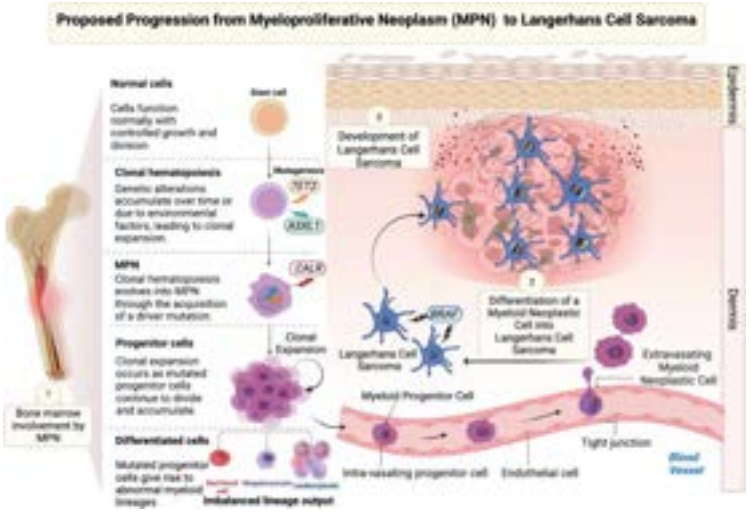
- **Can be primary or secondary**
  - Primary occurs de novo
  - Secondary arises from another neoplasm
    - Transdifferention from another hematolymphoid neoplasm
    - Anaplastic progression from low grade Langerhans cell histiocytosis





[image] Sadeghian et al. *Virchows Arch.* 2025 PMID: 40915985; WHO Classification of Tumours Haematolymphoid tumours 5th ed

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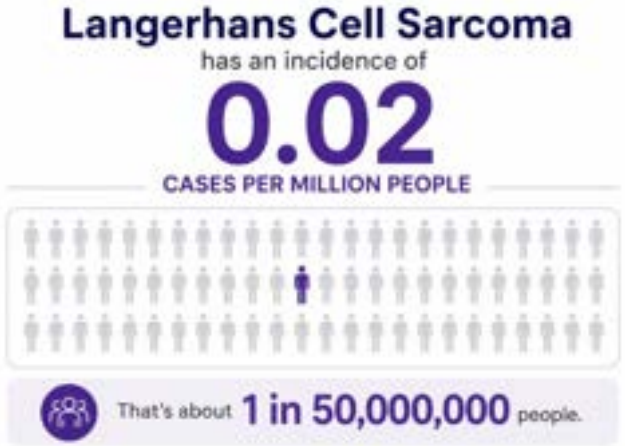
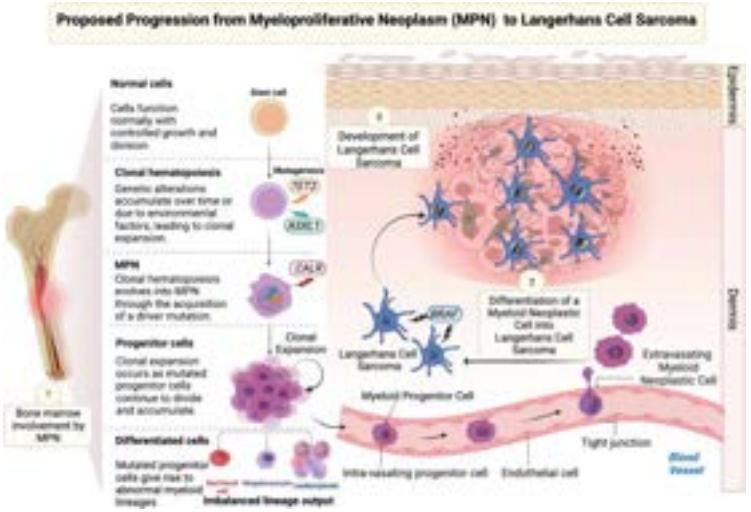
    - Anaplastic progression from low grade Langerhans cell histiocytosis

- Clinical symptoms depend on organ(s) involved
  - **Most commonly extranodal**, including skin, soft tissue, lung, bone
  - Single or multifocal presentation
    - ~45% multifocal, often include liver, spleen, lymph node and/or bone marrow
    - ~20% isolated lymph node involvement

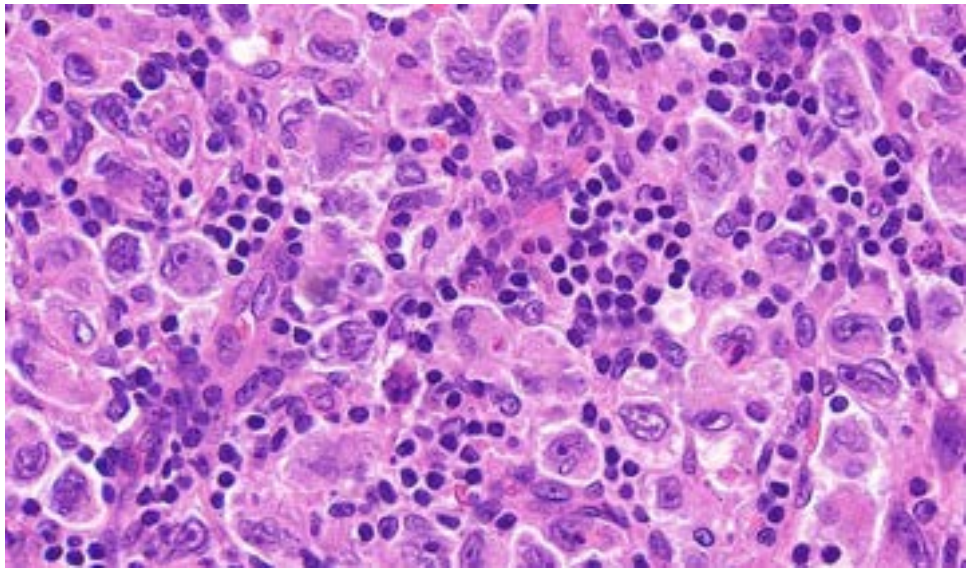


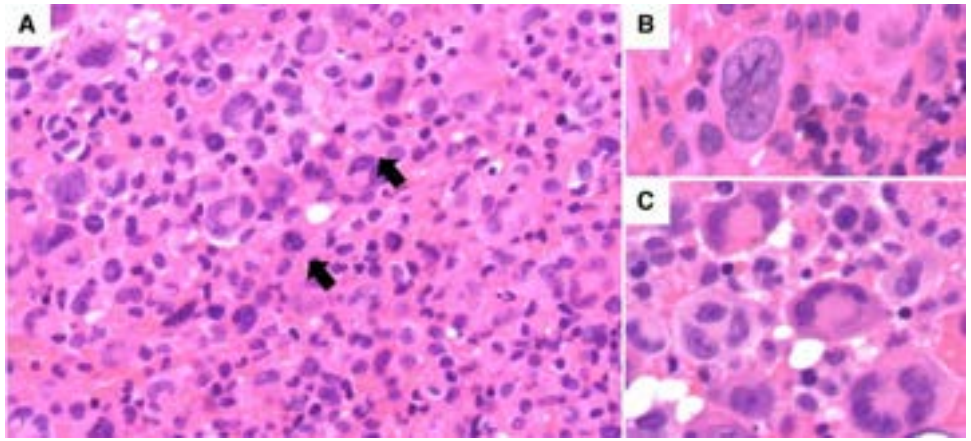


WHO Classification of Tumours Haematolymphoid tumours 5th ed

Morphology

- High grade cytology
  - Nuclear pleomorphism and anaplasia
  - Condensed chromatin prominent nucleoli
  - Frequent and/or atypical mitoses
  - Necrosis





[Lower Image] Dezzani et al. *Virchows Arch.* 2025 PMID: 40848146

Morphology

- High grade cytology
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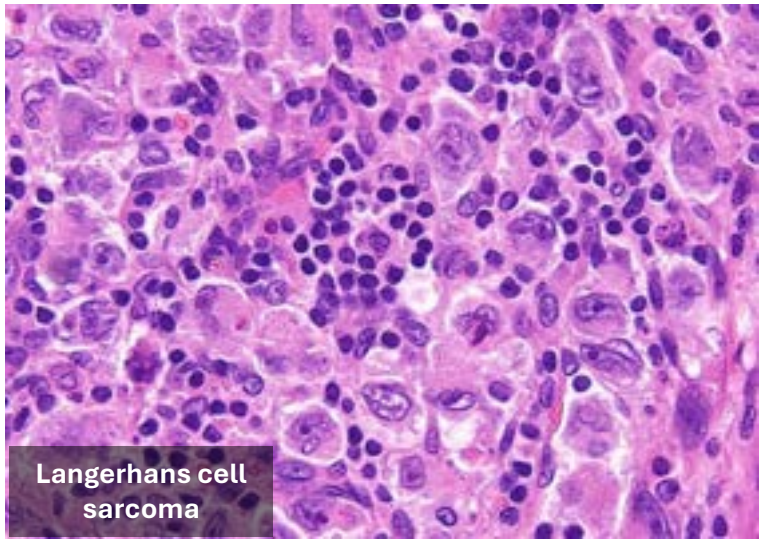
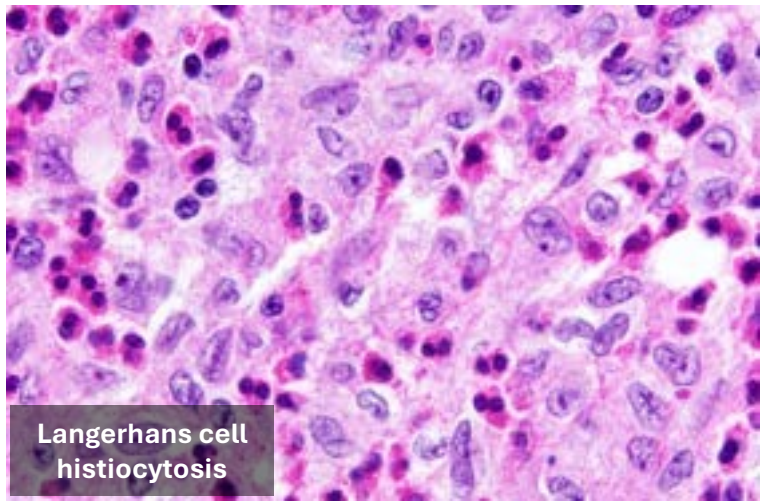
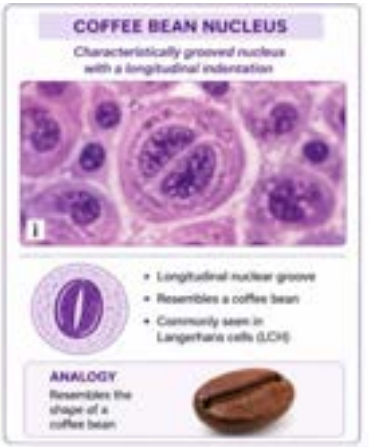
- Classic Langerhans cell morphologic features can be present (not always)
  - Elongated, grooved, convoluted nuclei
  - +/- Eosinophils


Langerhans cell sarcoma


Langerhans cell histiocytosis



[Images at right] ChatGPT generated

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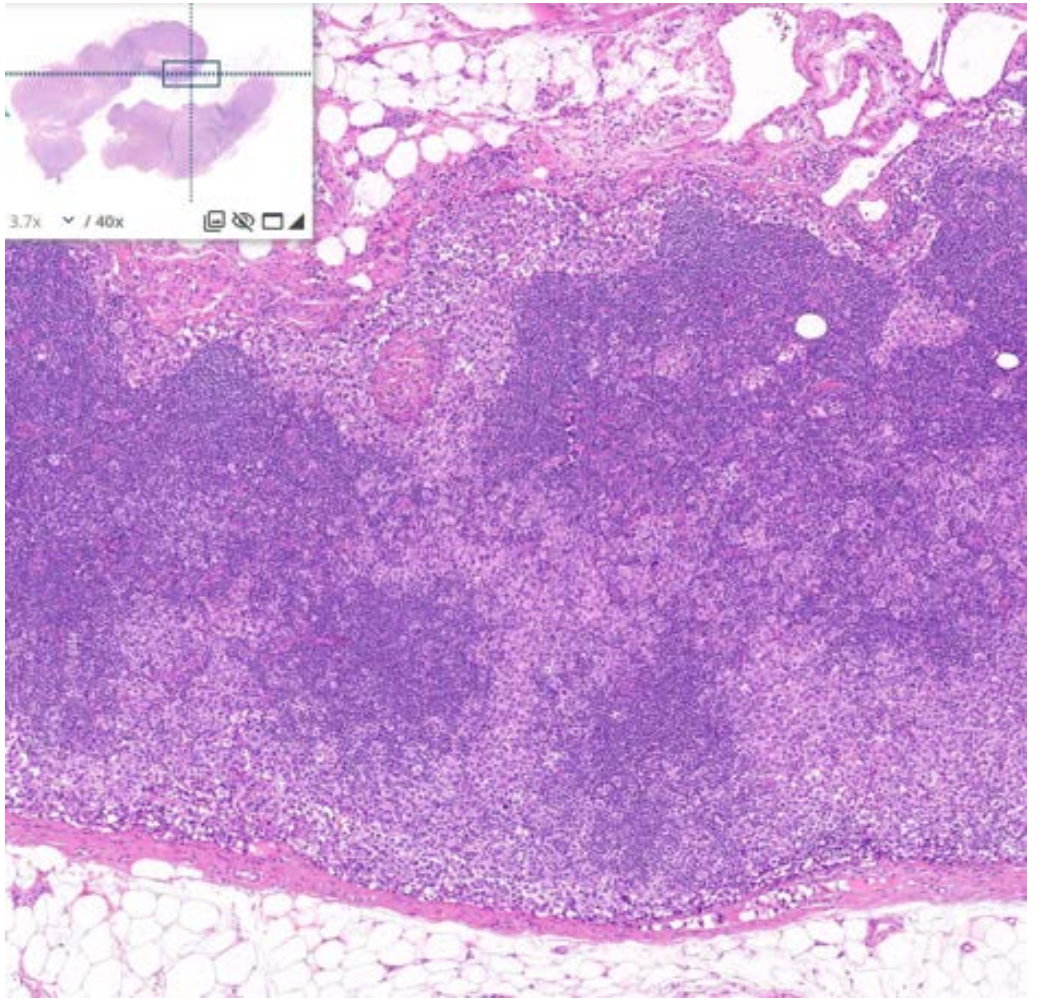
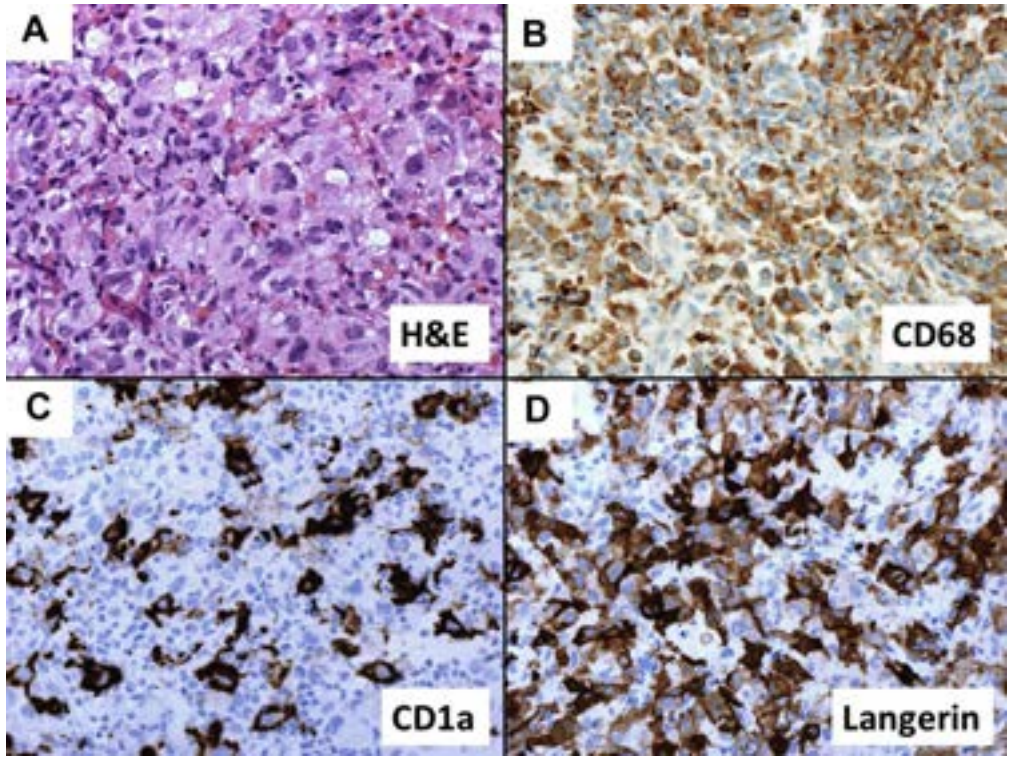
  - Elongated, grooved, convoluted nuclei
  - +/- Eosinophils
- Lymph nodes can have prominent sinusoidal distribution



Immunophenotype

- Requires evidence of Langerhans cell phenotype
  - EM showing **Birbeck granules**
  - IHC positive **dendritic cell** (CD1a, S100) and **Langerin/CD207**
  - **Staining can be focal / variable!**
    - Percentage for calling positive not well defined
  - **Important to assess staining on high-grade cells!**
    - Not background milieu



WHO Classification of Tumours Haematolymphoid tumours 5th ed; [image] Harsha Tella et al. *Clin Lymphoma Myeloma Leuk* 2019 PMID: 31005630)

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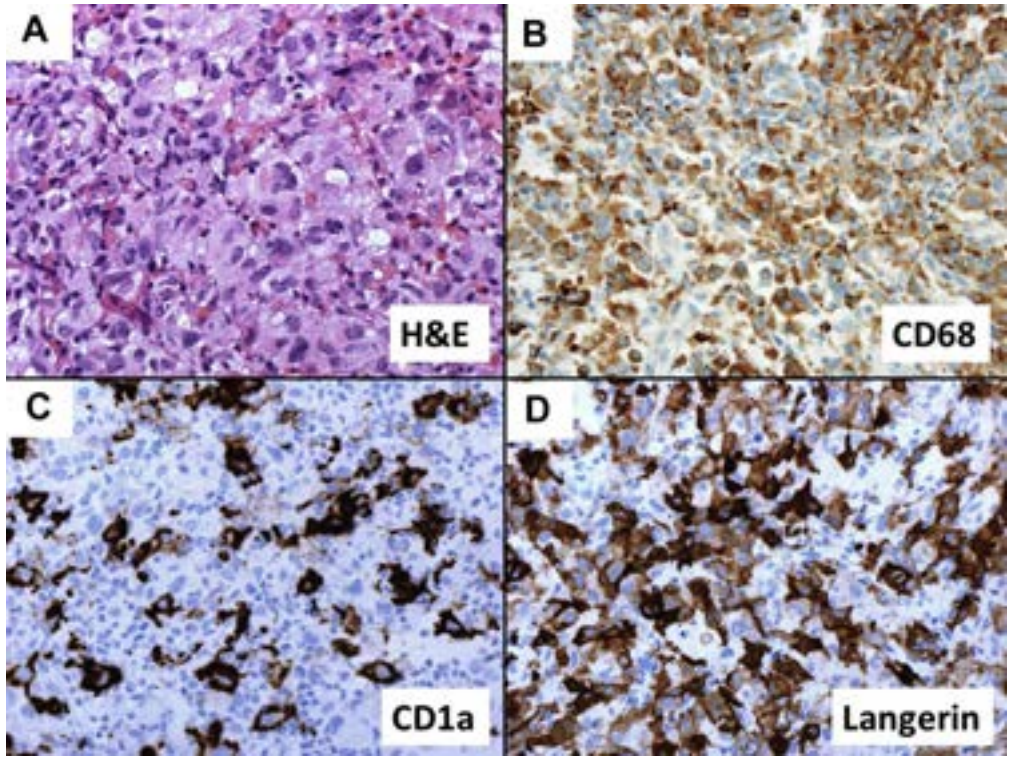
- Our case lacked CD1a, and had T cell antigens & BCL6
  - Rare reports of CD30, CD56, or T cell markers
  - Rare reports of BCL6 expression in cases secondary to B cell lymphoma



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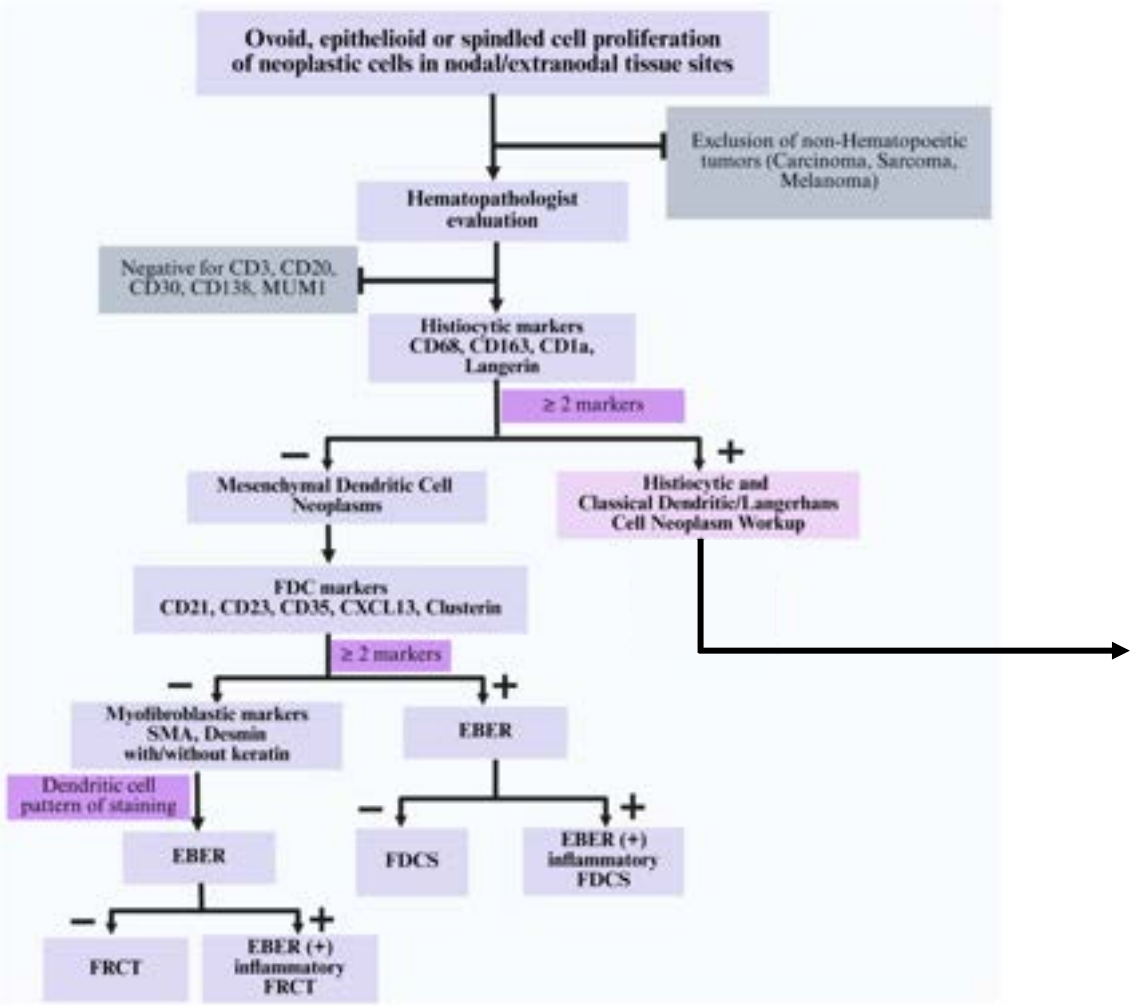
Immunophenotype & Differential diagnosis



[Image] Seth et al. *Cancers* 2025 PMID: 40563703

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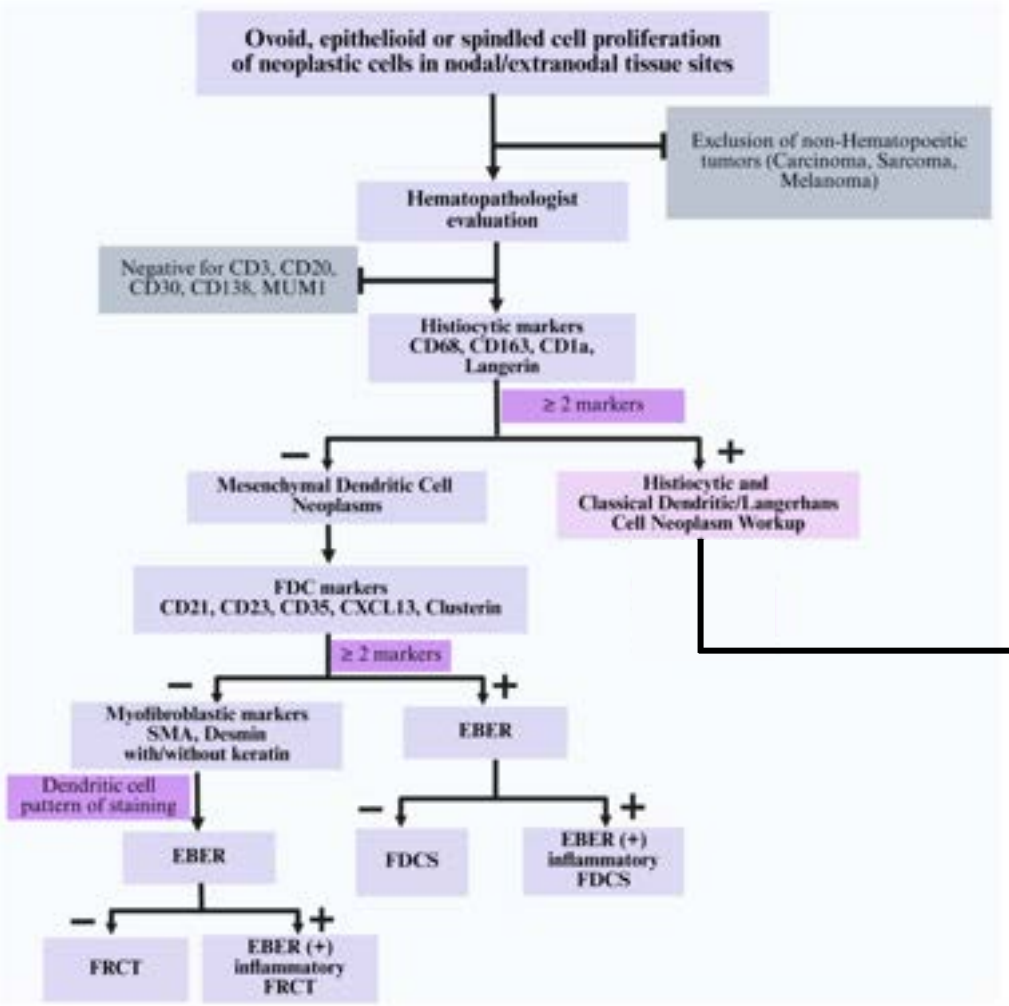

	CD68, CD163	S100	CD1a	Langerin (CD207)
Histiocytic sarcoma	+	+/-	-	-
Interdigitating dendritic cell sarcoma	+/-	+	-	-
Indeterminant dendritic cell tumor	+/-	+	+	-
Langerhans cell sarcoma	+	+	+	+

Be sure to exclude: reactive infiltrates, benign/indolent histiocytoses, myeloid sarcoma (immature chromatin, CD13, CD33, CD34, CD117, myeloperoxidase), plasmacytoid dendritic cell proliferations (CD123, CD303, TCL1A), etc.

[Image] Seth et al. *Cancers* 2025 PMID: 40563703; Pileri et al. *Histopathology* 2002 PMID: 12121233; WHO Classification of Tumours Haematolymphoid tumours 5th ed;

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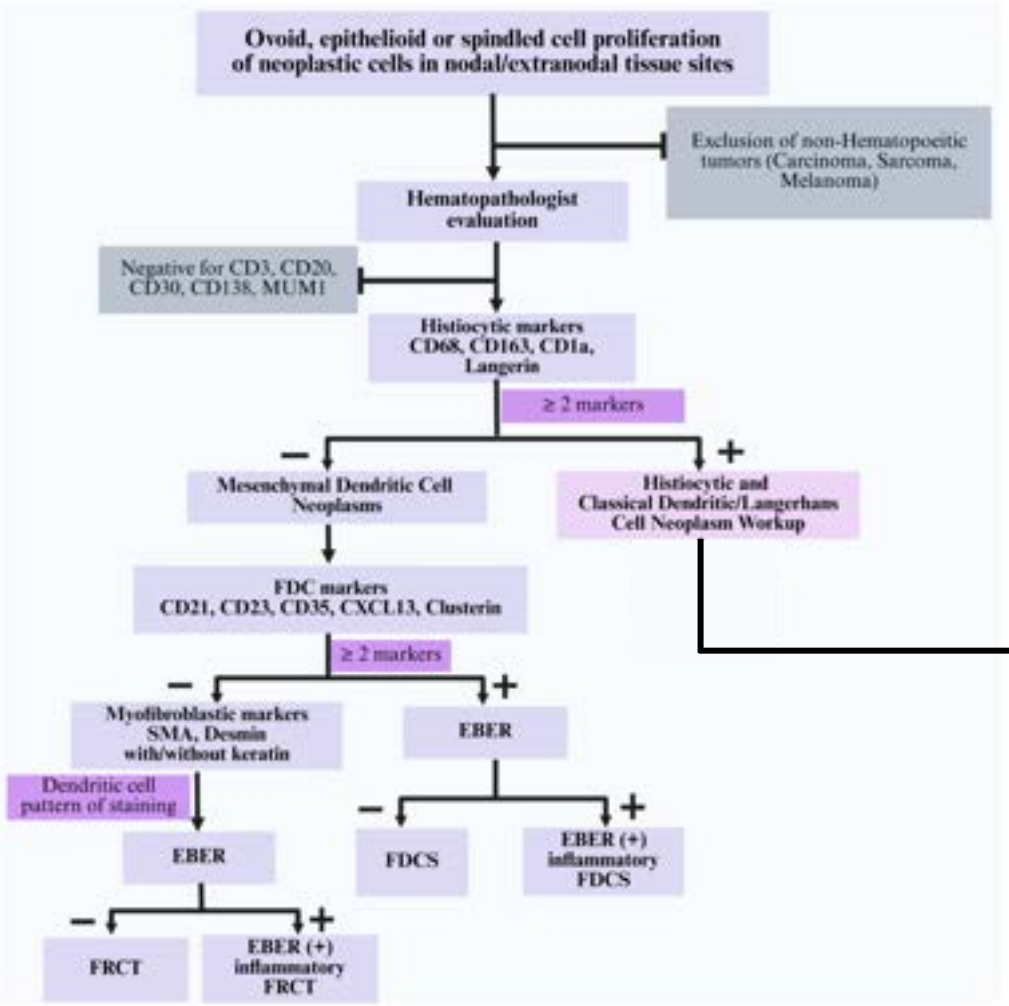

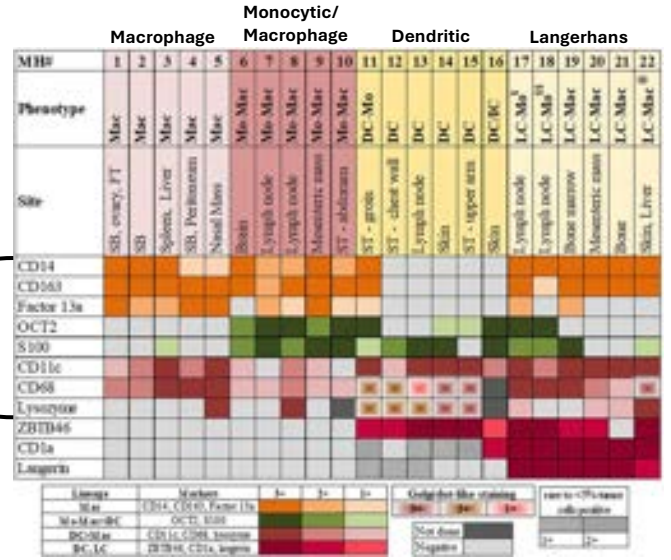

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[Image] Massoth et al. *Oncologist* 2021 PMID: 33904632; [Image] Seth et al. *Cancers* 2025 PMID: 40563703; Pileri et al. *Histopathology* 2002 PMID: 12121233

Molecular & Cytogenetic

- Clonal process with heterogeneous molecular and/or cytogenetic abnormalities

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- Massoth et al.(2021) study of M-group
  - MAPK mutations (*KRAS, MAP2K1, PTPN11, BRAF p.V600E* - less frequently than LCH)
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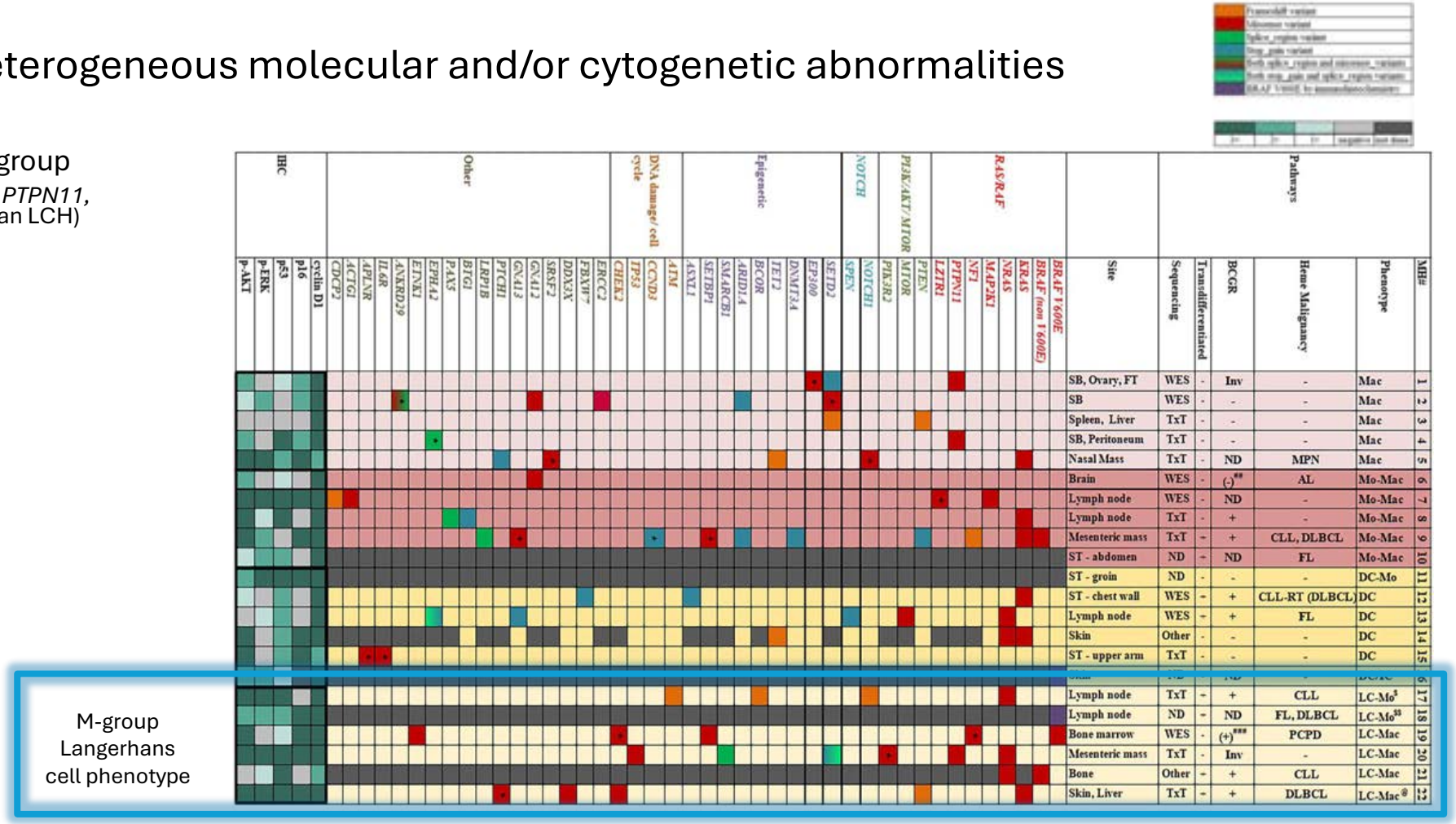

[image] Massoth et al. *Oncologist* 2021 PMID: 33904632; Dezzani et al. *Virchows Arch* 2025 PMID: 40848146

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- Dezzani et al. (2025) study of LCS
  - Signaling pathways (*BRAF, NRAS, PTPN11, KRAS, MAP2K1, NOTCH1, PTEN*)
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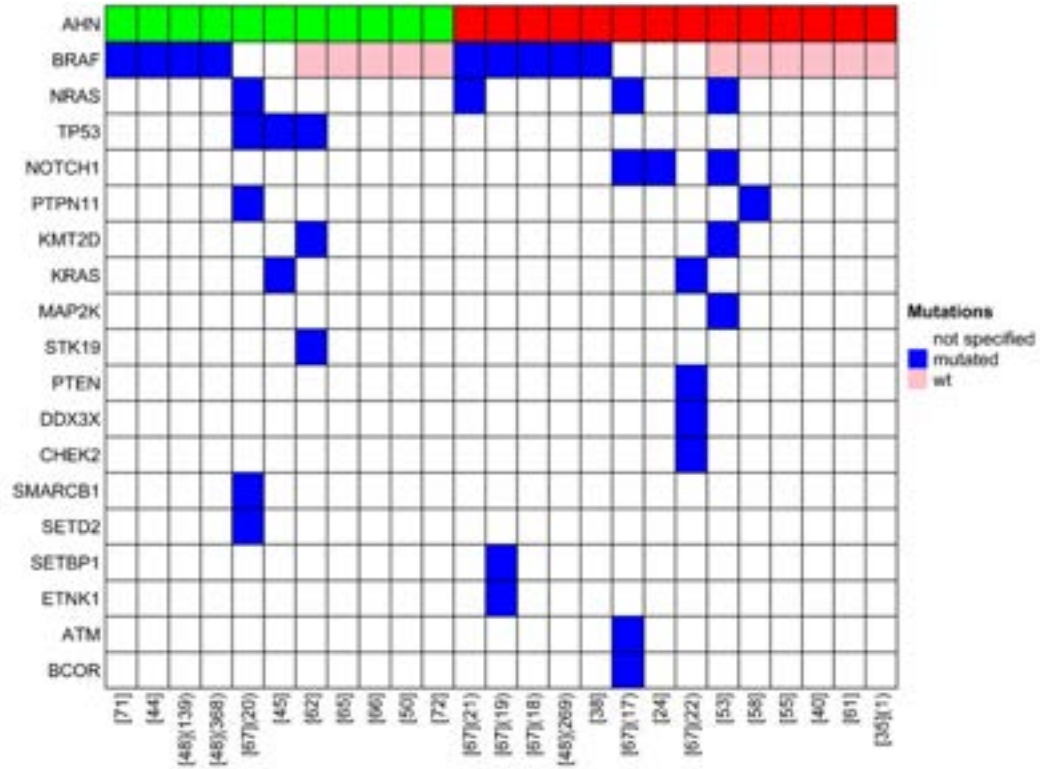
  - pERK pathways



Oncoplot depicting mutations observed in pLCS and LCS–AHN. The top row ("AHN") distinguishes pLCS cases (green) from AHN–LCS cases (red). Mutated genes are shown in blue, wild-type in pink, and white squares indicate tests not performed or not specified. Legend: LCS–AHN, Langerhans cell sarcoma associated with a hematologic neoplasm; pLCS, primary Langerhans cell sarcoma; wt, wild type

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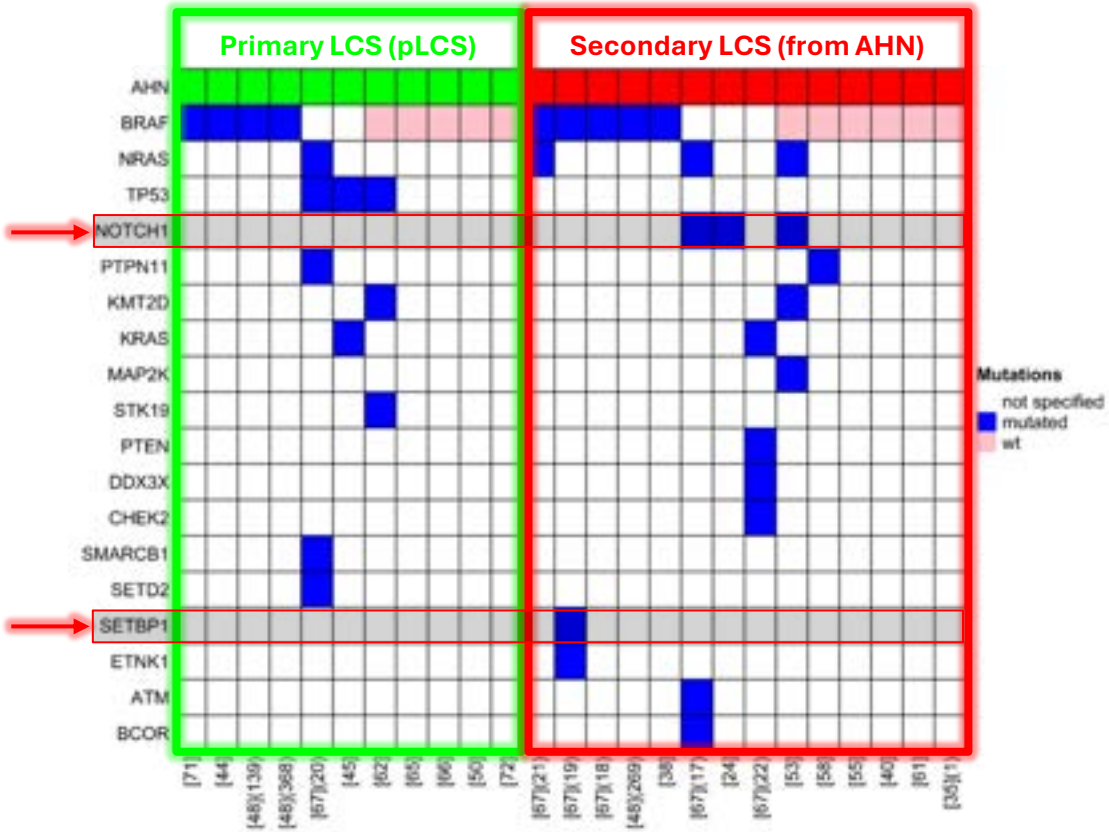
  - pERK pathways

- If secondary LCS
  - A clonal relationship can be supported by a shared mutational or chromosomal profile
  - Dezzani et al. (2025) showed LCS-AHN group was enriched in:
    - Mutations observed in lymphoid and myeloid neoplasms
    - Cytogenetic abnormalities



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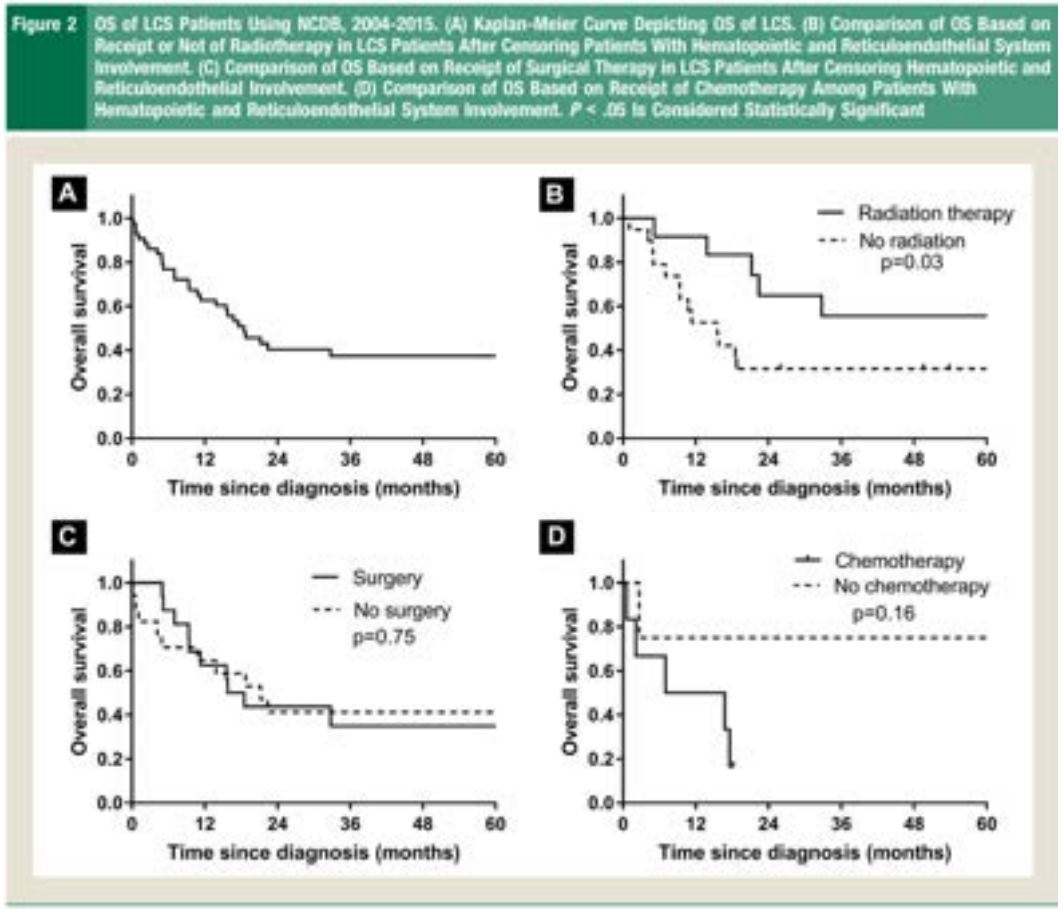
Prognosis & Treatment

- Aggressive disease, poor prognosis
  - Median survival time of 19–27 months

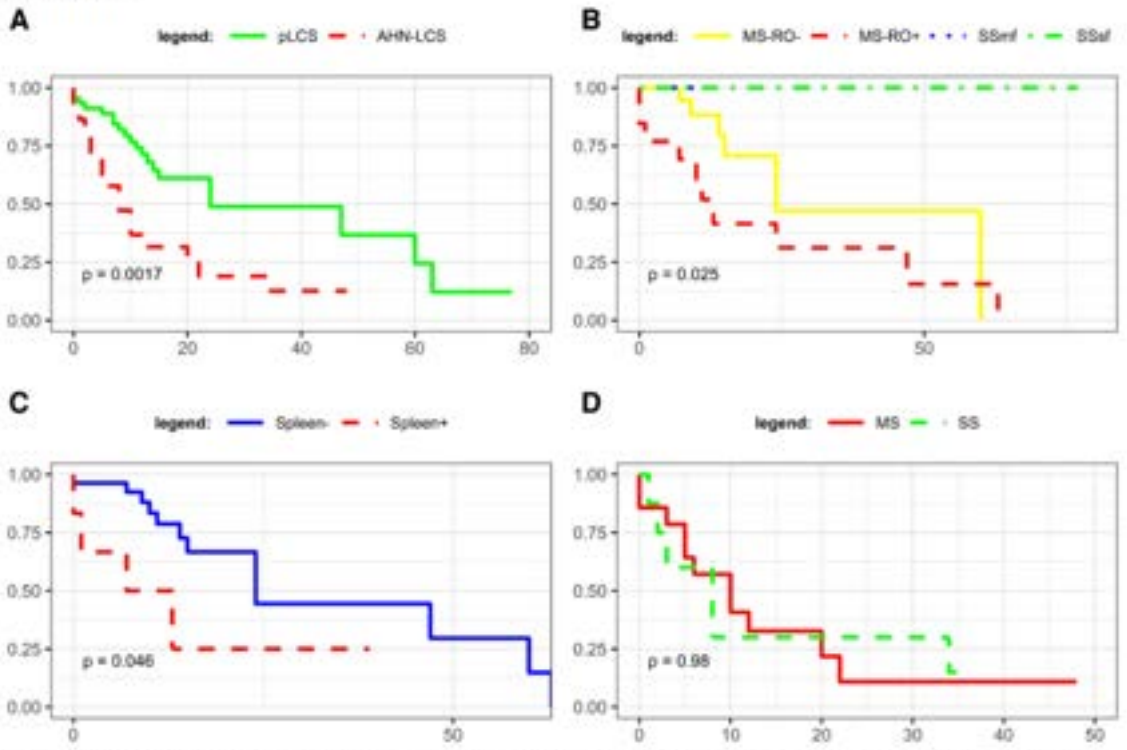


[image] Harsha Tella et al. *Clin Lymphoma Myeloma Leuk* 2019 PMID: 31005630;

Prognosis & Treatment

- Aggressive disease, poor prognosis
  - Median survival time of 19–27 months
  - Poorer prognosis
    - Secondary LCS with associated hematologic neoplasm
    - Multifocal/widespread disease

From: Langerhans cell sarcoma is a clinically, biologically, and prognostically heterogeneous "malignant" histiocytosis: a systematic review of 88 cases from the literature



Comparison of the overall survival between pLCS and LCS-AHN (A, $p = 0.0017$), pLCS patients divided according to disease spread (B, $p = 0.0254$), patients with vs without spleen involvement (C, $p = 0.0461$), and LCS-AHN patients divided according to disease spread (D, $p = 0.9783$). Legend: LCS-AHN, Langerhans cells sarcoma with associated hematological neoplasm; MSRO +, multisystem with risk organs involvement; MSRO-, multisystem without risk organs involvement; pLCS, primary Langerhans cells sarcoma; SSsf, single-system single focal; SSmf, single-system multifocal

[image] Dezzani et al. *Virchows Arch* 2025 PMID: 40848146

Prognosis & Treatment

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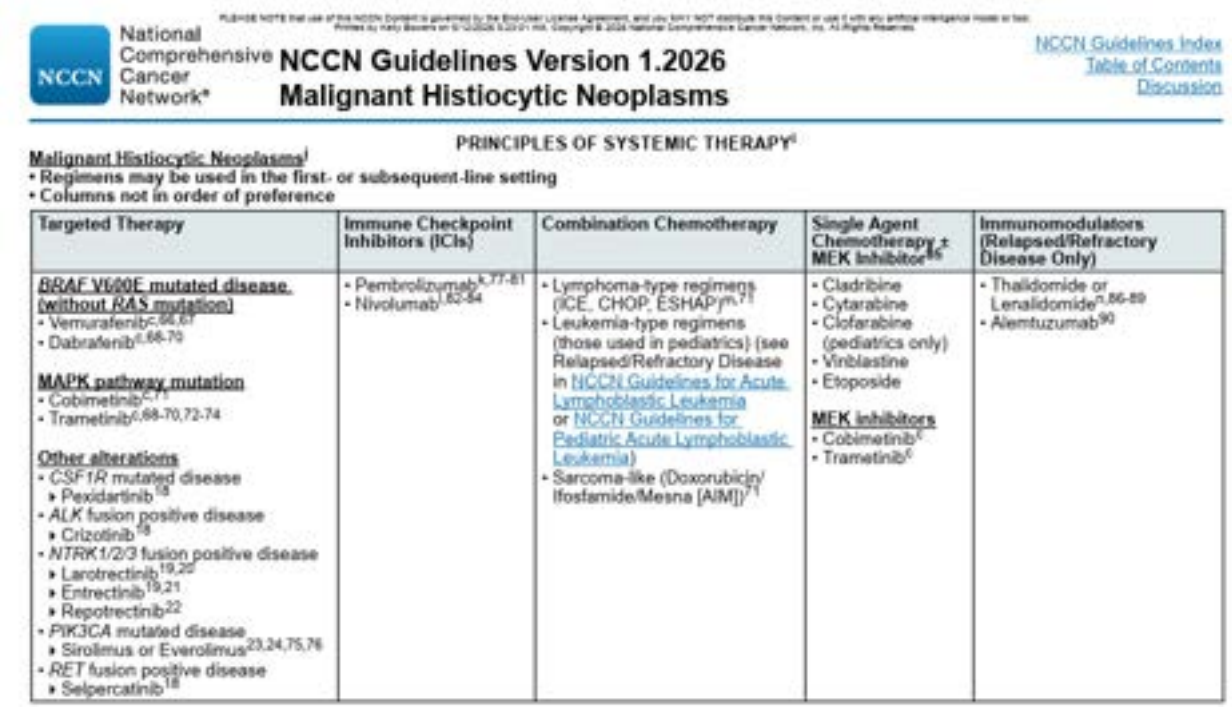
- Treatment includes
  - Surgical resection
    - Survival advantage in complete resection of localized disease
  - Radiotherapy
  - Chemotherapy
  - Targeted therapy
    - Anti-PD1 therapy, BRAF or MEK inhibitors, among others
  - Multi-modal therapy



National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2026
Malignant Histiocytic Neoplasms

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY[d]

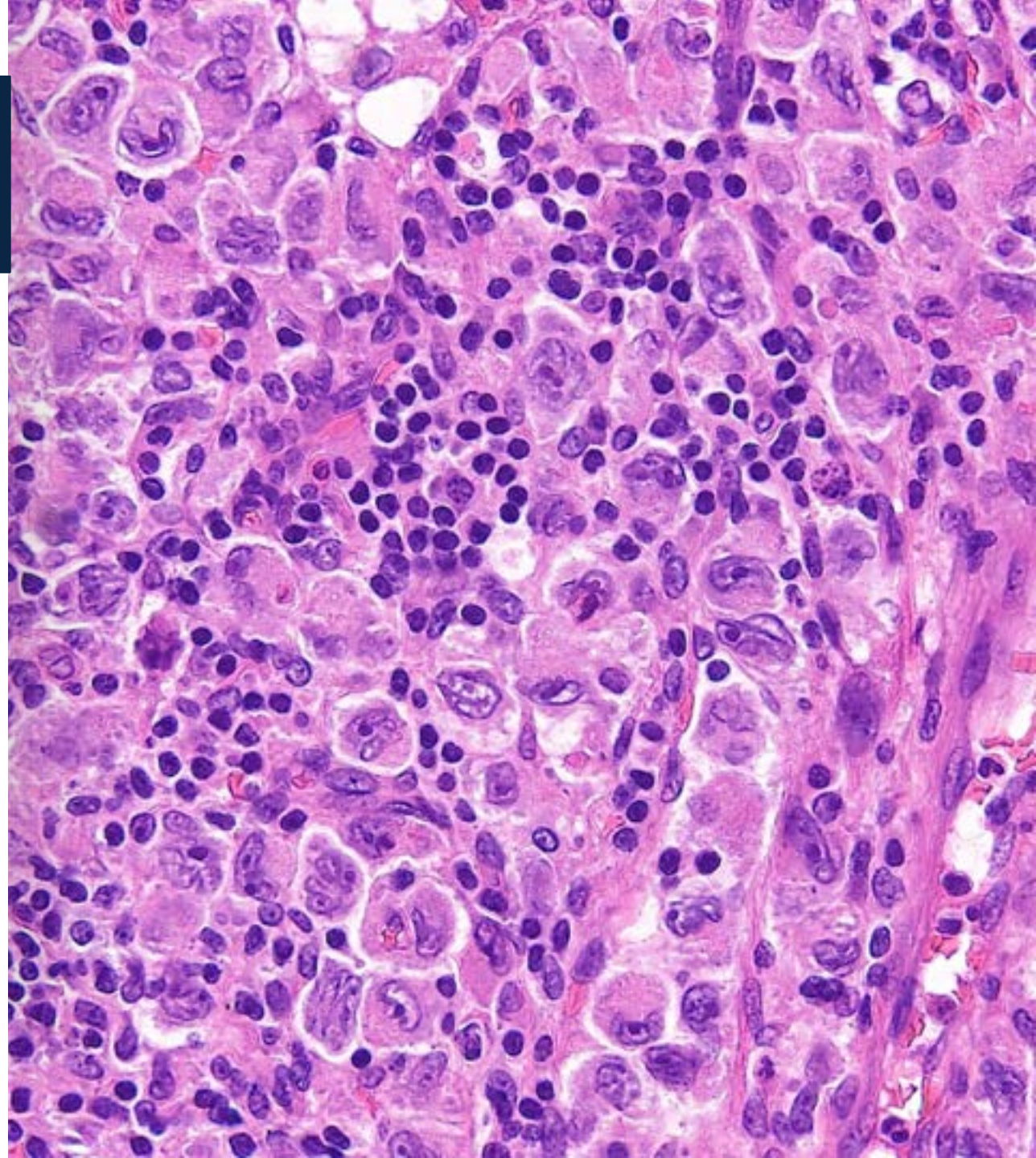
Malignant Histiocytic Neoplasms[i]
- Regimens may be used in the first- or subsequent-line setting
- Columns not in order of preference

Targeted Therapy	Immune Checkpoint Inhibitors (ICIs)	Combination Chemotherapy	Single Agent Chemotherapy ± MEK Inhibitor[85]	Immunomodulators (Relapsed/Refractory Disease Only)
***BRAF* V600E mutated disease (without *RAS* mutation)** • Vemurafenib[c,66,67] • Dabrafenib[c,68-70] **MAPK pathway mutation** • Cobimetinib[c,71] • Trametinib[c,68-70,72-74] **Other alterations** • *CSF1R* mutated disease › Pexidartinib[18] • *ALK* fusion positive disease › Crizotinib[18] • *NTRK1/2/3* fusion positive disease › Larotrectinib[19,20] › Entrectinib[19,21] › Repotrectinib[22] • *PIK3CA* mutated disease › Sirolimus or Everolimus[23,24,75,76] • *RET* fusion positive disease › Selpercatinib[18]	• Pembrolizumab[k,77-81] • Nivolumab[l,82-84]	• Lymphoma-type regimens (ICE, CHOP, ESHAP)[m,71] • Leukemia-type regimens (those used in pediatrics) (see Relapsed/Refractory Disease in NCCN Guidelines for Acute Lymphoblastic Leukemia or NCCN Guidelines for Pediatric Acute Lymphoblastic Leukemia) • Sarcoma-like (Doxorubicin/Ifosfamide/Mesna [AIM])[71]	• Cladribine • Cytarabine • Clofarabine (pediatrics only) • Vinblastine • Etoposide **MEK inhibitors** • Cobimetinib[c] • Trametinib[c]	• Thalidomide or Lenalidomide[n,86-89] • Alemtuzumab[90]

Take home points

- **Malignant histiocytoses** can be a diagnostic challenge
  - Morphologic overlap with high-grade / poorly differentiated neoplasms
  - Phenotype can be patchy, difficult to interpret from background milieu

- **Langerhans cell sarcoma** requires lineage, either Langerin IHC stain (can be focal!) or Birbeck granules by EM
  - Do not forget to look for an associated hematolymphoid neoplasm
  - Molecular studies are important to identify potential targeted therapies



Thank you

Cleveland Clinic